

THESIS
ON
FACTORS AFFECTING BLOOD FLOW
IN THE VISCERA

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by

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INTRODUCTION

A. REVIEW

In the living body, there is constant readjustment in the amount of blood flowing through different parts.

Claude Bernard (1851, 1852) first showed experimentally (in the ears of rabbits) that alterations in the blood flow can occur through the decrease or increase of the activity of the nerves supplying the muscles of the blood vessels. He proved subsequently (1858) that, as judged by the effect of cutting or stimulating the nerves on the vessel wall, two types of nerves are present in the body. (a) Vasoconstrictors which on stimulation reduce the calibre of the blood vessels and reduce the blood flow; (b) vasodilators which on stimulation increase the calibre of the blood vessels and increase the blood flow. He showed also that normally the tone of the muscles of the vessel wall is due to the vasoconstriction. Finally, he proved (1858) that reflex vasomotor effects generally appear in the vascular bed where the sensory excitation arises from. Thus, when the tongue is stimulated, the submaxillary gland flushes, so these reflexes are purposeful.

It would appear then, such reflex vascular responses when widespread may influence considerably the dynamics of the circulation, unless

controlled in an integrated manner in the body by compensatory mechanisms. As the total algebraic sum of vasoconstriction and vasodilatation of peripheral vessels determines the final total peripheral resistance, Loven (1866) considered it necessary to supplement Bernard's observations further by studying the interrelationship of such changes in the blood vessels and blood flow with the simultaneous alterations in the heart beat and blood pressure.

The results of his observations are summarised below.

- (a) Vascular responses can and do occur reflexly, by the stimulation of sensory nerves.
(Somatic sensory nerves were used.)
- (b) Either vasoconstriction and diminished blood flow or vasodilatation and increased blood flow or both may occur as reflex responses.
- (c) Vasoconstriction only, by increased resistance to blood flow, causes a rise in blood pressure. The heart beat gets slow when the blood pressure rises. This occurs reflexly via vagi.
- (d) When vasodilatation occurs, the blood pressure may or may not rise. But the blood pressure is never reduced. So it is suggestive of compensatory vasoconstriction occurring somewhere else in the body. When along with vasodilatation blood pressure is high, the

blood flow is increased considerably.

- (e) Such reflex vascular responses as can be observed are confined mostly to the vascular territory innervated by the nerve stimulated, or its adjacent area.

That, besides the somatic afferents, similar reflex pressure responses and vascular changes can be due to stimuli arising from visceral sites, was later shown by Mayer and Pribram (1872). They found that in dogs and cats, when the stomach is suddenly inflated, there is slowing of the heart and increase in the blood pressure. In 1878, Heidenhain and Grutzner compared the quantitative changes in blood pressure following the stimulation of different sensory nerves, both somatic and visceral. They found that the afferent fibres from the viscera produce the most marked vasomotor reflexes (pressure responses).

In 1871, the site of the vasomotor centre responsible for homeostatic control of blood pressure was found by Ludwig and Owsjannikow to occupy a space in the floor of the 4th ventricle and extending up from the apex of calamus scriptorius. Two years later, Dittmar showed that the centre is bilateral. The cardio-inhibitory or excitatory centre is also closely related to it. Therefore, the peripheral stimuli may reach both the vasomotor and cardiac centres simultaneously.

But Loven had already shown that increased or

decreased cardiac activity was not primarily a reflex response to the stimulus applied to the sensory nerve itself, but secondary to changes in blood pressure. So it was considered that in vascular reflexes all afferents, somatic or visceral, pass up via the posterior nerve roots to the vasomotor centre, and from there the efferents come down and are relayed via the spinal cord along the sympathetic vasoconstrictors or parasympathetic vasodilators. Spinal cord has ~~got~~ no independent active part to play in. Loven (1866) himself suggested this, even before the existence of a vasomotor centre was demonstrated, and he suggested that the changes in the heart rate are due to impulses sent from vasomotor centre to cardio-inhibitory centre and from there via vagi to heart.

In subsequent years it was shown that such reflex vascular responses can be widespread in the body (Ranvier).

Bradford (1899) carried on an interesting series of experiments in which he observed the reflex vascular changes following the stimulation of central ends of the sensory roots of the spinal nerves in segmental levels. He found that the stimulation of lower dorsal roots produces more marked splanchnic vasoconstriction than that produced by the stimulation of upper dorsal roots (as judged by the volume changes in renal or intestinal vascular capacity). He showed also that greater

changes of arterial blood pressure are evoked by excitation of the posterior roots of thoracic nerves than stimulation of the peripheral nerves. Recently, Bors and French (1952) have observed similarly. In four patients undergoing posterior rhizotomy, the blood pressure readings indicated higher values during the handling of the thoracic and upper lumbar roots than those of the lower segments.

Sherrington was at this time engaged in studying the behaviour of the spinal animals. He found that, following the transection of the spinal cord (lower cervical or upper thoracic level), there is a variable period of acute spinal shock, varying in duration in different animals - smaller duration in the lower species and longer duration in the higher species. This stage of acute spinal shock is characterised by a state of very low blood pressure. But following this period of shock, the blood pressure rises to the level previous to transection, and vasomotor reflexes also return. As the site and the kind of the stimulus influence the reflexes obtained, Sherrington analysed critically the various reflexes that can be obtained from such spinal preparations only, as compared with those obtained by identical stimuli in the integrated nervous system, working as a complete unit.

In his Marshall Hall Prize Lecture, Sherring-

ton (1899) related his experience gained from these spinal animals, and stressed on the importance of the spinal cord in various vasomotor reflexes including the visceromotor one. Spinal cord had already been shown to be segmentally arranged anatomically, and Sherrington pointed out that functionally too spinal cord may be considered in segmental fashion, and visceral stimulation may be interpreted differently in different levels, depending on the short or long reflex arcs. In chronic spinal cats, he demonstrated that the arterial blood pressure rises when the common bile duct or the ureter is "distended adequately". Sherrington also suggested that pain is only one of the various reflex responses that can be obtained as a result of visceral distension. Suprasegmental levels are concerned with the interpretation of pain, and the rest of the responses can be mediated through the spinal cord.

Later on, it was shown, and thus Sherrington's view was partly confirmed, that vasomotor centre in the spinal cord can work independently of the suprasegmental control, and vasomotor reflexes can be mediated through the isolated cord (Kaya and Starling, 1909-10; Mathieson, 1910-11; Brooks, C.M., 1933, 1935; Alexander, R.S., 1945).

But further investigations into viscerovascular reflexes were neglected, and it appears from the literature that the experimental or

clinical physiologists became interested in the problem of visceral pain and reflex responses to visceral stimuli other than circulatory changes. Perhaps this was a result of influence of the importance of clinical observations, e.g. hyperalgesia and muscular rigidity in patients with intestinal obstruction, ureteric or biliary colic. The work of Brodie and Russell (1900-01), who confirmed the findings of Mayer and Pribram (1872), established the existence of a reflex response to impulses carried by pulmonary branches of vagi. The influence of clinical observation on this type of work from the case report they present provides the reason why they were interested in the phenomenon of reflex cardiac inhibition.

At the end of the First World War, Head and Riddoch (1917) in their classical paper confirmed the original idea of Sherrington's that visceral sensations are mediated through the spinal cord and in a segmental pattern. Sweating as a response to distension of urinary bladder or intestine was found as a constant and reliable clinical response in such studies.

Subsequent investigations in this field, both experimental and clinical were also directed to find out other reflex responses. Results of these observations are summed up in the following, along with their uses.

(a) The dilatation of the pupil and the con-

traction or relaxation of the nictitating membrane are now recognised as indices of reflex responses to visceral stimulation in animal investigation (Ashkenaz and Spiegel, 1935).

(b) Interrelationship of different viscera can now be explained by viscerovisceral reflexes (Denny-Brown and Robertson, 1933; Boyden and Rigler, 1934; Hermann and Morin, 1934; Morin and Vial, 1934; Lalich, Meek and Herrin, 1936; Youmans, Meek and Herrin, 1938; Youmans, Karstens and Aumann, 1941-42; Svien and Mann, 1943). I personally feel that viscerovisceral reflexes will have a great future in explaining the mechanism of chronic dyspepsias, associated with chronic appendicitis or cholecystitis, in which flatulence, in particular, is a marked clinical feature.

(c) That somatic structures, the skin and the muscles of the abdomen or lower limbs, can be affected reflexly by distension of the viscera has also been clearly shown by both experimental and clinical investigations (Miller and Simpson, 1925; Miller and Wand, 1925; Mackenzie, 1919, 1920; Morley, 1931). In connection with cutaneous hyperalgesia, Wernoe (1920, 1925) observed "anaemic zones" in Head hyperalgesic areas during the attacks of visceral pain. He considered it to be due to a sympathetic postganglionic reflex.

Some of these reflexes have also been shown to occur in spinal animals. These experimental and

clinical investigations have, however, proved conclusively:-

(1) Distension is the ideal stimulus (Hurst, 1911; Kappis, 1913; MacKenzie, 1919; Frolich and Mayer, 1922; Payne and Poulton, 1927; Schrager and Ivy, 1928; Ryle, 1929; Bloomfield and Pollard, 1931).

(2) To produce effects, distension must be adequate.

(3) Reflex responses due to visceral stimuli can be mediated through the spinal cord and such may be of segmental types.

(4) Pain is only one of the various reflex responses. There may be other reflex manifestations.

While a remarkable progress has thus been achieved in the studies of different reflex responses to visceral stimuli, a curious and more interesting feature in the history of physiology in the last 15 years has been a gradual return or switch over of such investigations to changes in cardiovascular activity. A brief but compact review about the reflex cardiac activity, including the coronary blood flow, has been written by Scherf and Boyd (1948). Reference is also made to the classical paper of Ray and Neill (1947) for visceral sensations, particularly pain.

Talaat (1937) found that in anaesthetised dogs severe distension of the urinary bladder caused a rise in blood pressure from 15 to 30 mm.Hg. Cutting

the pelvic visceral nerves had no effect on this pressor reflex, while cutting the hypogastric nerves completely abolished it in 3 preparations and greatly reduced it (to 5 mm.Hg.) in two others.

Watkins (1938) showed in the anaesthetised cat a rise in blood pressure on distension of the urinary bladder. Downmann, Goggio, McSwiney and Young (1943-44) found in the same animal vasoconstriction of paws as a reflex to visceral stimulation. Continuing investigations, Downman and McSwiney (1946-47) found that both viscerovascular and viscerosomatic reflexes can be demonstrated in acute spinal preparations, and they considered that spinal preparations are most suitable for eliciting such reflex responses. The difficulties in excluding the somatic stimuli arising simultaneously in the mesentery, when a portion of the jejunum or ileum is distended, were considered. By carefully planned experiments, Downman, McSwiney and Vass (1948) proved conclusively that intestines have a sensory nerve supply anatomically and physiologically distinct from that of the adjacent mesentery.

In clinical physiology, similar observations have now been available. Carmichael, Doupe, Harper and McSwiney (1939) found that vasomotor reflexes can be demonstrated in man on distension of the duodenum with balloon. Vasoconstriction was found to occur in toe vessels more frequently

than in finger vessels, and such findings were obtainable even when no subjective sensation as pain was present. Sturup (1940) found in cases of appendicitis that, although pain was not actually present, there were areas of hyperalgesic pallor even in the lateral parts of the segments.

The first valuable contribution on the visceral spinal reflexes, and their manifestations by sweating, was made by Head and Riddoch (1917) in their investigations in the paraplegics at the end of the First World War.

After the Second World War, Guttman and Whitteridge (1947) reported their investigations into the effects of urinary bladder distension to sweating and cardiovascular activity, in particular blood pressure and peripheral blood flow in paraplegic patients. They observed when the urinary bladder is distended:-

- (a) there is a rise in systolic and diastolic blood pressure; this is more and more pronounced as the lesion extends higher up in the thoracic segments.
- (b) such changes in blood pressure are primarily related to intravesical pressure.
- (c) when the lesion is at or below T₆, there is vasoconstriction in toes but vasodilatation in the fingers. When the lesion is at or above T₅, there is vasoconstriction in both the fingers and the toes.

The gravity of this problem of viscerovascular reflexes is also now being realised in the different fields of clinical physiology. Both the physiologists and clinicians agree that vasomotor reflexes initiate and maintain the morbidity described as "Dumping Syndrome". The rise in both systolic and diastolic blood pressure, and many of the clinical features seen during these attacks, have been reproduced experimentally by Machella (1949) in man, by distending a balloon in the duodenum. His observations are, however, still incomplete. Adams-Ray and Norlen (1951) found that on distension of urinary bladder in man, bilateral pallor in the dorsal segments 11 and 12 can be produced. They showed that bilateral sympathectomy (T_{11} and T_{12}) abolish this pallor. They considered that such viscerocutaneous reflexes are mediated in the spinal cord.

But the fact that the viscerovascular reflexes play a profoundly disturbing effect in the "Homeostasis of blood pressure" has only clearly been demonstrated now by Guttman and Whitteridge (1947). The clinical syndrome of "dumping" illustrates amply also how the viscerovascular reflexes can incapacitate the individual. It is unfortunate that in spite of a tremendous literature on the "dumping syndrome" very little information is available regarding vasomotor reflexes and even a systematic study of blood pressure changes during

the attacks.

Whitteridge and his colleagues have now established on a sound basis that viscerovascular reflexes are mediated through the spinal cord and, therefore, what Sherrington conceived, spinal cord could be considered as an independent vasomotor unit though subject to suprasegmental influence in the integrated nervous system. So far, however, no work has been done in the past to analyse how and why there is a reflex increase in blood pressure. In other works, the effector mechanism of reflex blood pressure changes has not been explored at all before. Feeling this, Cunningham, Guttman, Whitteridge and Wyndham (1953) continued their investigations on paraplegics and observed that the changes in cardiac output were not significant enough to account for this rise in blood pressure. Skin and muscle blood flow in the upper and lower limbs were studied in these patients. As the changes were quantitatively not sufficient to account for the changes observed, the latter authors raised the question of splanchnic vasoconstriction as a possibility or one of the possibilities responsible for the rise in peripheral resistance and the resultant rise in blood pressure.

Feeling that the rise in intravesical pressure may seriously interfere with the blood flow to the bladder wall and mucosa, they suggested that the purpose of rise in systemic blood pressure may be

to maintain the adequate blood flow through the distended viscus. Therefore, the importance of investigations into the blood flow through the bladder as it gets distended was also stressed by them.

Though the findings of Guttman and Whitteridge (1947) have been subsequently confirmed by Thompson and Witham (1948); Pollock, Boshes, Char, Finkelman, Arieff and Brown (1951); Schumacher and Guthrie, (1951); Bors and French (1952), no information has yet been available either from clinical or from experimental physiology about the problems raised by the latter authors (Cunningham, Guttman, Whitteridge and Wyndham, 1953) as to the role of splanchnic vascular bed to account for rise in blood pressure or the effect of bladder distension and rise of blood pressure on the bladder blood flow.

B. PURPOSE AND PLAN OF THE PRESENT WORK

The primary purpose of undertaking experimental work was to investigate ~~into~~ these aspects.

To reproduce "paraplegic" conditions in which Whitteridge and his colleagues have carried on investigations, it seemed desirable to use chronic spinal preparations. But chronic spinal animals are extremely difficult to nurse. As Watkins (1938) and McSwiney and his colleagues (1943-48) have already obtained satisfactory results using non-

spinal and acute spinal preparations, the present studies have been confined to these preparations only.

Urinary bladder was selected for distension, for the following reasons:-

- (a) Its afferents are carried by L_1 and L_2 and S_2 , S_3 and S_4 and, therefore, splanchnicectomies will not interfere with the afferent arc.
But it would help experimentally to find out whether viscerovascular reflexes affect the aplanchnic vascular bed or not.
- (b) The urinary bladder was used for distension in the paraplegics by Guttman and Whitteridge (1947).
- (c) With minimal intra-abdominal handling, the ureters can be tied quickly, and the urethra can be cannulated through the space of Retzius (Retropubic space), and the bladder can be put back and the abdomen closed.
- (d) Watkins has already obtained definite vasomotor responses by the distension of the urinary bladder.

As the present work is partly concerned with the previous work of Watkins (1938), his work will now be considered in further relevant points, and then the progress of the work as done in this laboratory will be reported.

Watkins (1938) has found that when the urinary bladder of an anaesthetised cat is

distended, there is a rise in arterial blood pressure. He has also shown that this is primarily related to intravesical pressure. But at the same intravesical pressure, there were marked fluctuations in the quantitative changes of blood pressure. Cutting the vagi, the depressor nerves and tying the adrenals did not alter this reflex response. Examining the curve showing relationship of vesical volume to changes in blood pressure (Watkins, 1938), it appears that at the same pressure head perhaps the fluctuations were due to different volumes of fluid in the bladder and therefore different degrees of stretching, or may have been due to biological variations in individual animals or due to differences in the experimental conditions which have not been discussed. When the fluid in the bladder exceeded 80 ml., the fluctuations in the quantitative changes of blood pressure rise (in Watkins' series) is very marked. It is a fact, however, that the capacity of urinary bladder of cats varies from animal to animal. It seems that filling the bladder to 80 ml. or more at a pressure head (60 mm.Hg.) may have been harmful to the viscus itself and, therefore, the responses differed widely. Various anaesthetics were also tried in these experiments, and Watkins observed that the anaesthetics had no influence on these reflex responses. Watkins also found that when both hypogastrics and pelvic splanchnics are

cut, the reflex response disappeared, but not so when either one is cut. (Cf. Talaat, 1937)

Whether the difference in findings obtained by Talaat (1937) and Watkins (1938) is due to the species difference has not been investigated yet.

From preliminary experiments in two cats under ethylchloride, ether and chloralose anaesthesia, it was found:-

(a) A demonstrable (by mercury manometer and kymograph) rise in arterial blood pressure always occurs when the urinary bladder is distended at 65 mm.Hg. pressure head. At 45 mm.Hg. or between 45 and 65 mm.Hg. pressure, blood pressure increases very little and sometimes may not rise at all, unless the bladder is stretched by distending with fluid more than 80-100 ml.

(b) Rapid distension of urinary bladder (Cf. Watkins - 80 ml. in 10 secs.) is harmful because the returning fluid is always tinged red indicating haemorrhages in the bladder wall.

(c) Distension of urinary bladder to 80 ml. in one cat caused rupture of the vessels in the bladder wall, and when the bladder was emptied the haematoma spread. The capacity of urinary bladder in cats of different sizes and body weights was investigated, and it was found to vary from 60-100 ml. usually a small bladder in small sized ones and a big one in larger sized cats.

The capacity of the urinary bladder is

determined in the following way. The bladder is connected to an overhead reservoir (containing normal saline at 37°C.) by a cannula put in the urethra. It is allowed to be distended slowly at a rate of 5 - 8 ml./minute. The pressure head used varies from 45-65 mg.Hg. As the bladder fills up, the tube connecting the reservoir to the bladder is clamped occasionally. The bladder surface is examined. It is also palpated gently. When the bladder becomes tense, hard and remains so, any further attempt to fill it forcibly causes rupture of the vessels in its wall. The capacity of the bladder is then considered as the amount just necessary to distend it to the stage before the blood vessels rupture. The returning fluid from the bladder on decompression is also examined. If it is tinged red, it is taken for microscopical examination. On one occasion red blood cells were seen when the bladder was being filled very rapidly (80 ml. in 10 seconds). Rapid decompression is also undesirable. The above procedure is carried out by keeping the bladder intraabdominal/y.

(d) The interesting finding, however, was that the rise in arterial blood pressure following distension of urinary bladder at the same rate, was much more marked in the animal after vagotomy and carotid sinus denervation than in the other one where vagi and carotid sinus nerves were intact. As the primary purpose of the present work was to

study circulation in the splanchnic vascular bed and the bladder, this observation appeared worth while for further investigations with the view that in the nonspinal preparations vagotomy and carotid sinus denervation may be an essential prerequisite to study viscerovascular reflexes. Ten experiments were carried out. The results of these have been discussed in Chapter 1. Attempts have been made, before and after splanchnicectomy, to find out such changes if the splanchnic vasoconstriction is predominantly the factor responsible for increase in peripheral resistance and, therefore, causes rise in arterial blood pressure when urinary bladder is distended. Bilateral splanchnicectomy abolished the responses completely. The results of pre- and post-splanchnicectomy experiments have been discussed in Chapter 1.

Before starting investigations into the splanchnic and urinary bladder vascular bed, a few experiments were done to find out (a) the relation of rate of filling to the lag phase before the rise in blood pressure; (b) to the relation between the rise in blood pressure and continuously increasing the volume of the bladder at the same pressure head; (c) changes in blood pressure by repeating experiments in the same animal with or without varying the rate of distension. Experiments were also repeated by keeping the bladder outside to study whether the same responses can be obtained.

Usually following chloralose, the blood pressure remains high for 30-45 minutes. Immediately following vagotomy and carotid sinus denervation, a very high blood pressure is obtained. The results of distension of bladder on the changes of blood pressure when it is already high, will also be reported.

These have been discussed in Chapter 1. These were done with the main purpose of finding out (a) conditions suitable for eliciting vascular reflexes following distension of hollow viscera, (b) suitable rate of distension, (c) suitability of repeating experiments in the same animal, (d) to show variations from the majority of findings.

When it was found that bilateral splanchnicectomy abolishes the reflex vasomotor responses, that can be obtained before such procedure, it was a definite proof, indicating that splanchnic vasoconstriction is a predominant mechanism in the rise of blood pressure.

But the primary purpose of undertaking this experimental work, as stated before, was to investigate the role of splanchnic vascular bed in the viscerovascular reflexes by direct measurements of splanchnic volume flow. The difficulties encountered in such investigations had first to be considered. The splanchnic nerves (sympathetic) supply a large vascular bed which can be morphologically considered in mainly four components:

(i) gastrointestinal (ii) splenic (iii) hepatic (iv) renal. It was obvious that it is impossible to measure blood flow or study circulatory changes in splanchnic vascular bed as a whole by any single technique. As it is quite possible that all the four vascular beds may not show identical or unidirectional changes, it would also be better to investigate each one separately. The renal vascular bed was first chosen for the following reasons.

(a) The left kidney can be exposed extra-peritoneally and thus intraabdominal manipulation is avoided.

(b) Renal circulation has been of considerable interest in the last few years because of the great role played by the kidney in the readjustment of blood volume in the body (Van Slyke, 1951-52).

Though it was felt that actual measurement of renal blood flow will be ideal, for the present purpose the changes in renal pulses and renal volume have sufficed. A plethysmographic technique has been used. A technique of measuring renal blood flow is being attempted.

Studies on renal circulation proved further that when the urinary bladder is filled at a pressure head of 65 mm.Hg. at a rate of 60 ml./min., there is vasoconstriction and as filling progresses there is a diminution in the volume of renal pulses. This will be discussed in Chapter 2. Here also,

it was noticed that such changes in the renal circulation are less marked before vagotomy and carotid sinus denervation.

This finding, along with the previous one obtained in the studies on blood pressure changes, suggested strongly that vagi and carotid sinus nerves form a path with the suprasegmental vasomotor centre, to exercise inhibitory influences over the splanchnic vasomotor centre in the spinal cord.

To verify it finally, experiments were carried out to observe the immediate effects of vagotomy and carotid sinus denervation on renal and renal pulse volumes. The results confirmed the previous findings. These suggest strongly that there is normally a reciprocity of the supra-segmental vasomotor centre and spinal cord splanchnic vasomotor centre working via the blood vessels and blood pressure and check nerves. This will be discussed in Chapter 3.

Simultaneously, attempts have been made to observe changes in paw volume if any. The results will be shown and discussed in Chapter 2.

Acute spinal preparations have also been investigated into the suitability of studying visceral vasomotor reflexes. In Chapter 4 the results that have been obtained in spinals will be presented and discussed.

Preliminary experiments on spleen and intestinal loops and bladder have also been made. Further are in progress.

CHAPTER 1

METHODS

Female cats varying in body weight from 2 - 3.5 kg. have been used. In the preliminary investigations, ether was used to induce anaesthesia. Later on, always ethylchloride has been used instead. The anaesthesia is maintained for a few minutes by whiffs of ether while chloralose solution (80 mgm/kg. B.W. and 1% soln. in N saline) is freshly prepared and then finally injected slowly via the saphenous vein. Ether administration is stopped while the injection of chloralose is commenced.

Immediately after the injection of chloralose, trachea is cannulated and a 3-way T-tube put in. The animal is kept warm at about 37°C, by alternately heating and cooling the table (thermometer being used to measure body temperature rectally).

By a midline incision $2\frac{1}{2}$ -3 inches long, extending up from pubic symphysis, skin and linea alba are cut. The recti are retracted laterally; the bladder is at once in view. Turning the bladder gently to either side, the ureter near its entrance into the bladder is seen. The blood vessels sweep over to the bladder wall along the terminal part of each ureter (near its junction with the bladder), and the ureters are always tied about $\frac{1}{2}$ inch higher up. Two double ligatures are applied and the

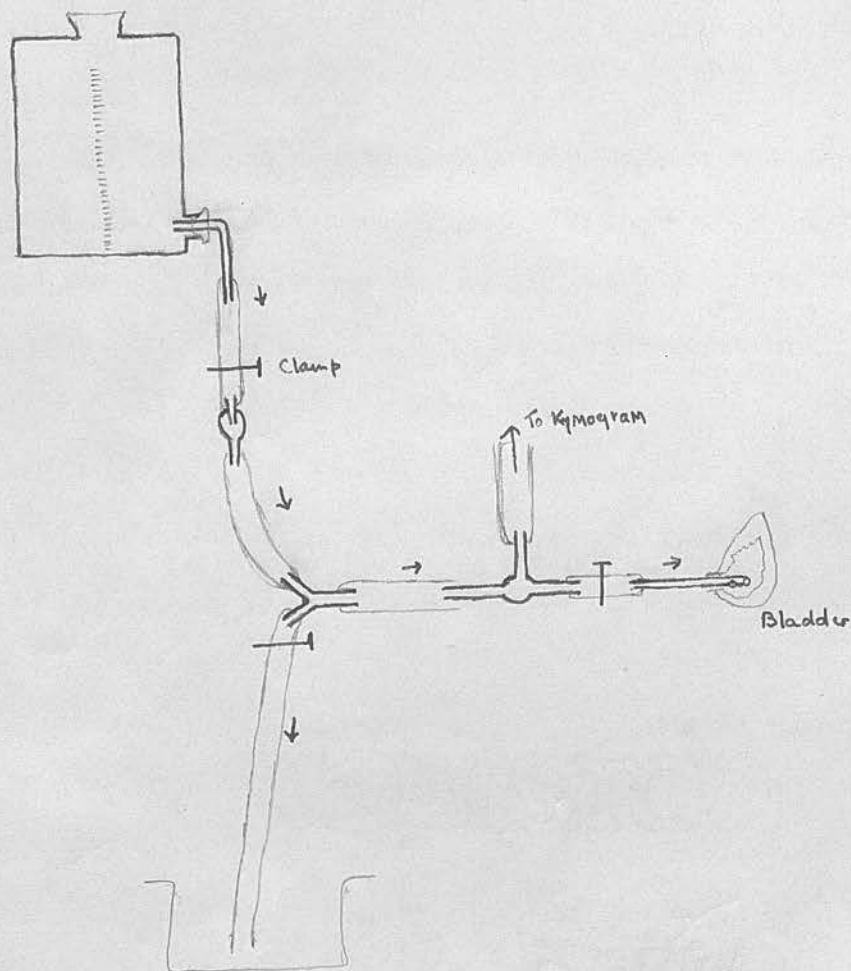
ureter is cut in between. Then a needle cannula connected with a polythene tube is put into the proximal stump of the ureter to drain the kidney. It is better to use unglazed threads as ligatures, because glazed linen threads always get loose and come out.

When both ureters have been tied, the thin serous membrane connecting anterosuperior surface of bladder to anterior abdominal wall is cut between ligatures. This thin serous coat does contain some fine blood vessels.

Then the bladder is retracted gently posteriorly and upwards and the urethra is identified in the middle line in the mesh of fat, straight down from the bladder neck to pubic symphysis. With minimal careful dissection, the urethra is cleared of periurethral tissue and, without damaging the blood vessels coursing up along it to the bladder, it is cannulated near the bladder neck, the distal stump being closed off by a ligature. The terminal end of cannula lies within the bladder.

The bladder connexion to the overhead pressure bottle is shewn in the diagram.(page 25)

The polythene tube is used to cannulate the bladder because it can be moulded without inconvenience to fit into the varying depth at which the urethra lies in the space of Retzius. It has got a lateral hole in addition to the terminal one to facilitate flushing in and out. Normal saline at



- a temperature varying from $36 - 38^{\circ}\text{C}$ is used for filling the urinary bladder. The pressure bottle used is such that changes in capacity of 100 ml. change the height in the fluid column by 20 mm. only.

The right femoral artery is cannulated and connected to Hg. manometer.

The anticoagulant used is S.S. Magsulph, and before the cannula is put into the artery, a few drops of liquaemin (diluted, 1/100) are put into

the cannula through the side tube.

The bladder pressure and the blood pressure are simultaneously recorded in the kymograph after carefully adjusting, so that the points of the stylets of both recording systems are in the same vertical line.

In the experiments to be described, the rate of filling the bladder has been 60 ml./minute. Sometimes a rate of 90-120 ml./minute has been used while repeating the experiments in the same animal. The pressure head used in filling the bladder has varied from 45-65 mm.Hg.

In the technique of vagotomy and carotid sinus denervation, particular care has been taken to free the common carotid^{*}, internal and external also (in first $\frac{1}{2}$ "), from all the periadventitial tissues. Usually following chloralose anaesthesia, the blood pressure remains high. So, in cleaning the sinus region and also the area below it, the fine muscular branches of the vessels, which are entwined amongst the slender nerve filaments, have to be treated individually and carefully. It has been found advantageous to put a bulldog clip on the common carotid and to proceed on to the dissection (the clamp being released gently, at intervals to flush the vessels and to tie the

In cats, the internal carotid branch at its origin looks like ascending pharyngeal one in man.

bleeding points that have been overlooked). Small pellets of cotton wool soaked in warm (N) saline, held in the point of dissecting forceps, are excellent mops for cleaning as well as separating the nerves gently from neurovascular bundles in the carotid zone. When the denervation of carotid sinus region is complete and the vagus is cut (usually below the larynx), the animal is watched for a few minutes (preferably 15-20 minutes), and then the procedure is carried out in the other side.

Before starting the bladder distension, all precautions are taken to see that no bleeding point has been left unligated. This is because the preliminary experiments have given a lasting lesson that, when the urinary bladder is distended and the blood pressure rises, any bleeding point overlooked and not tied becomes a source of continuous oozing and haematomas form quickly. In this connexion, stress should be laid upon the tiny venules, the branches of external jugulars, which are often torn and escape notice. A spreading haematoma has been observed in the neck from these sources on two occasions.

Splanchnic nerves are exposed extraperitoneally by an incision in each lateral abdominal wall, extending from the kidney angle to anterior superior iliac spine. Following the termination of each experiment, dissection is done to confirm that splanchnics handled were the real splanchnic nerves.

RESULTS

For the sake of convenience, the findings which have been obtained in the majority of the experiments will be mentioned first, and then the variations. According to the similarity, these have been grouped as follows:-

Group A (vagi and carotid sinus nerves intact)

In individual experiments, when the urinary bladder is distended at a pressure head of 65 mm.Hg. and at a rate of 60 ml./min., the reflex response as shewn by the rise of blood pressure is of the following types:-

- (i) Very poor response - little rise in blood pressure (Fig. 1).
- (ii) Slight response - 10% rise in blood pressure (Figs 2 and 3).

At 45 mm.Hg. pressure head, usually no response is obtained. In two experiments only, about 10% rise in blood pressure could be brought about, and in both of these almost similar changes in blood pressure were seen when 65 mm.Hg. pressure head was also used. Fig. 2 shows one of these.

Looking at Figs. 2 and 3, it will be seen that the blood pressure starts to rise after a certain period (lag phase) from the onset of filling of the bladder.

During the filling phase, the rise in blood pressure is slow but gradual in Figs. 2 and 3, and also intermittent in Fig. 3. When the filling is

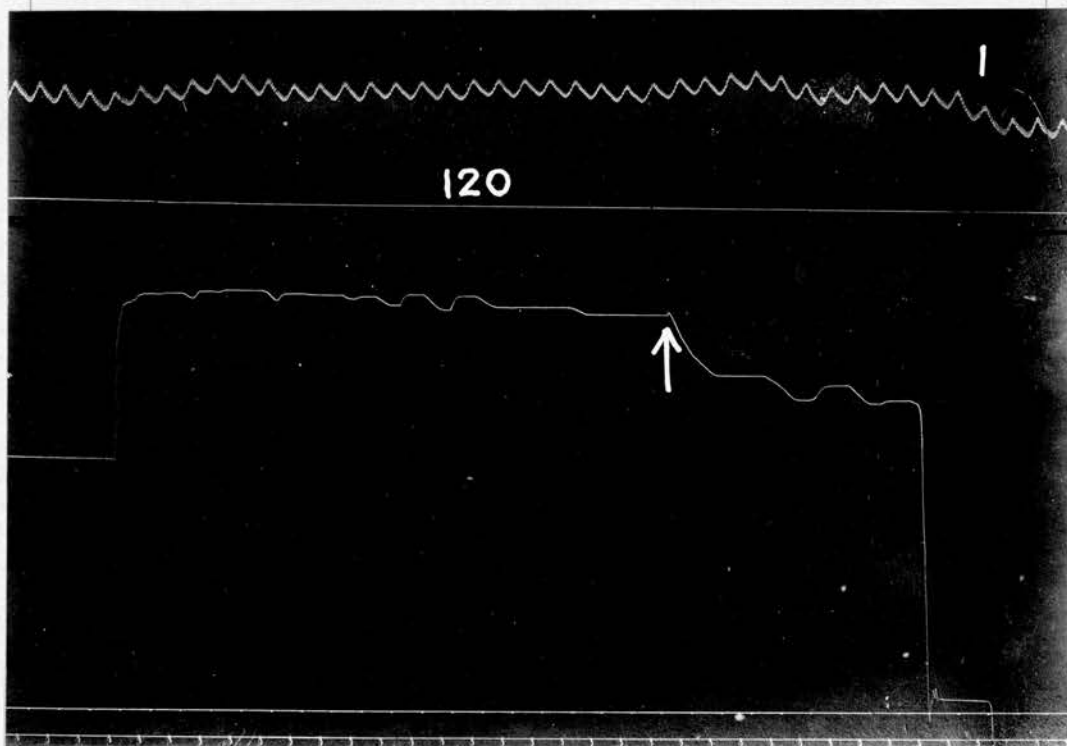


Figure 1

Before vagotomy and carotid sinus denervation.

Upper tracing blood pressure.

Lower tracing bladder pressure (65 mm.Hg.)

Arrow indicates filling stopped.

Time 5 seconds.

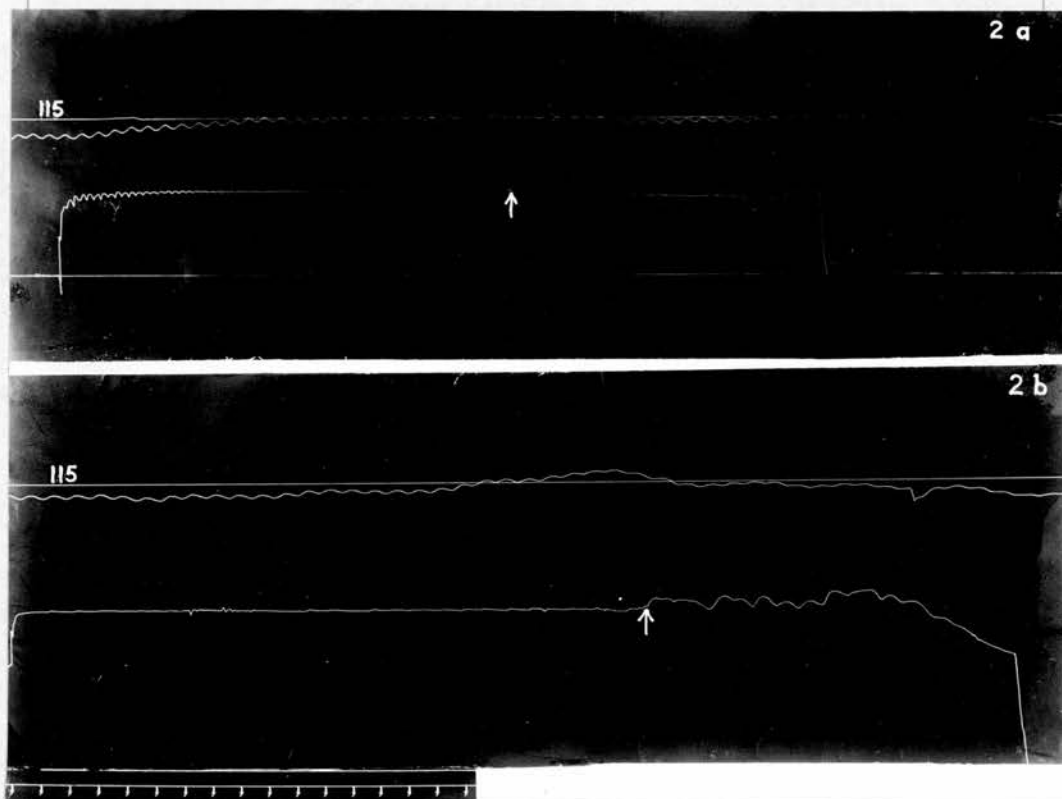


Figure 2

Before vagotomy and carotid sinus denervation.

Upper tracing in each - blood pressure.

Lower tracing - 2a Bladder pressure 65 mm.Hg.
 2b " " 45 mm.Hg.

Time 5 seconds. Arrows indicate when filling
 was stopped.

Note: Even when intravesical pressure remained
 the same, after filling was stopped, the
 blood pressure did not rise any more (cf.
 Fig. 6). Blood pressure starts falling as
 emptying starts and returns to original level.

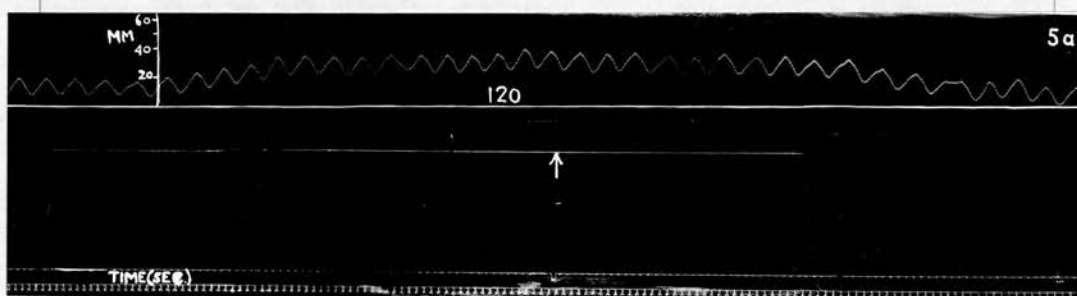


Figure 3

Before vagotomy and carotid sinus denervation.

Upper tracing blood pressure.

Lower tracing bladder pressure (65 mm.Hg.)

Time second.

Arrow indicates when filling was stopped.

Note: Rise of blood pressure is not a continuous slope. Blood pressure does not rise when filling is discontinued, though intravesical pressure remains the same.

stopped and the bladder is kept distended, the blood pressure does not rise but starts falling even if the intravesical pressure now remains the same as before (i.e. during filling)(Figs. 2 and 3).

The blood pressure starts falling if the intravesical pressure falls below the level at which it was during filling (Fig. 2b). Finally, when the bladder is emptied, the blood pressure comes down and returns to its prefilling level within 5-15 seconds.

When the experiments are repeated, almost identical findings are obtained. As yet, no depressor response has been obtained (cf. Watkins, 1938) Group B (vagi cut and both carotid sinuses denervated)

In individual experiments, when the urinary bladder is distended at a pressure head of ⁴⁵⁻65 mm.Hg. and at a rate of 60 ml./min., the reflex responses as shewn by the rise of blood pressure are of the following types:-

- (i) Rise in blood pressure always more than 15% (Fig. 4).
- (ii) Frequently there is a 25 - 30% rise, even when the experiments are repeated (Fig. 5).

At 45 mm.Hg. pressure head, occasionally there may be no response. But usually a slight rise in blood pressure is more frequent when compared to results obtained in the previous group.

Looking at Figs. 4, 5 and 6, it will be seen in

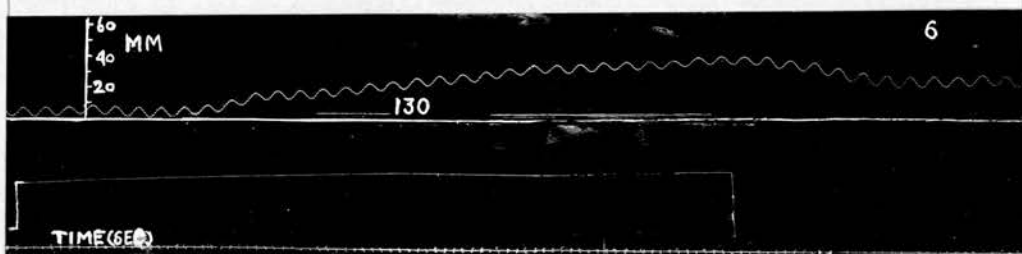


Figure 4

After vagotomy and carotid sinus denervation.

Upper tracing blood pressure.

Lower tracing bladder pressure (45 mm.Hg.)

Time (seconds).

Note: At the same pressure head, as filling is continued, blood pressure rises continuously and progressively (a linear slope). Blood pressure starts to fall immediately when bladder is emptied and does not return to the same level within the time period shown.

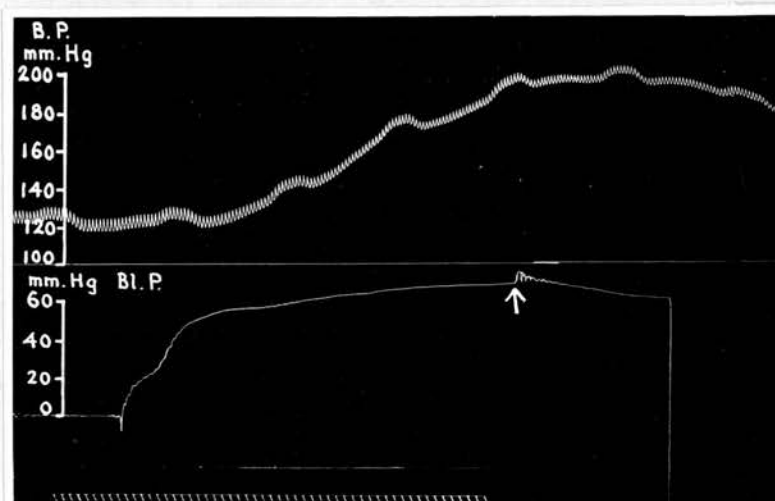


Figure 5

Effect of bladder distension on blood pressure.
(After bilateral vagotomy and carotid sinus
denervation)

B.P. - Blood pressure

Bl.P. - Bladder pressure

Arrow indicates - Filling stopped.

Time - second.

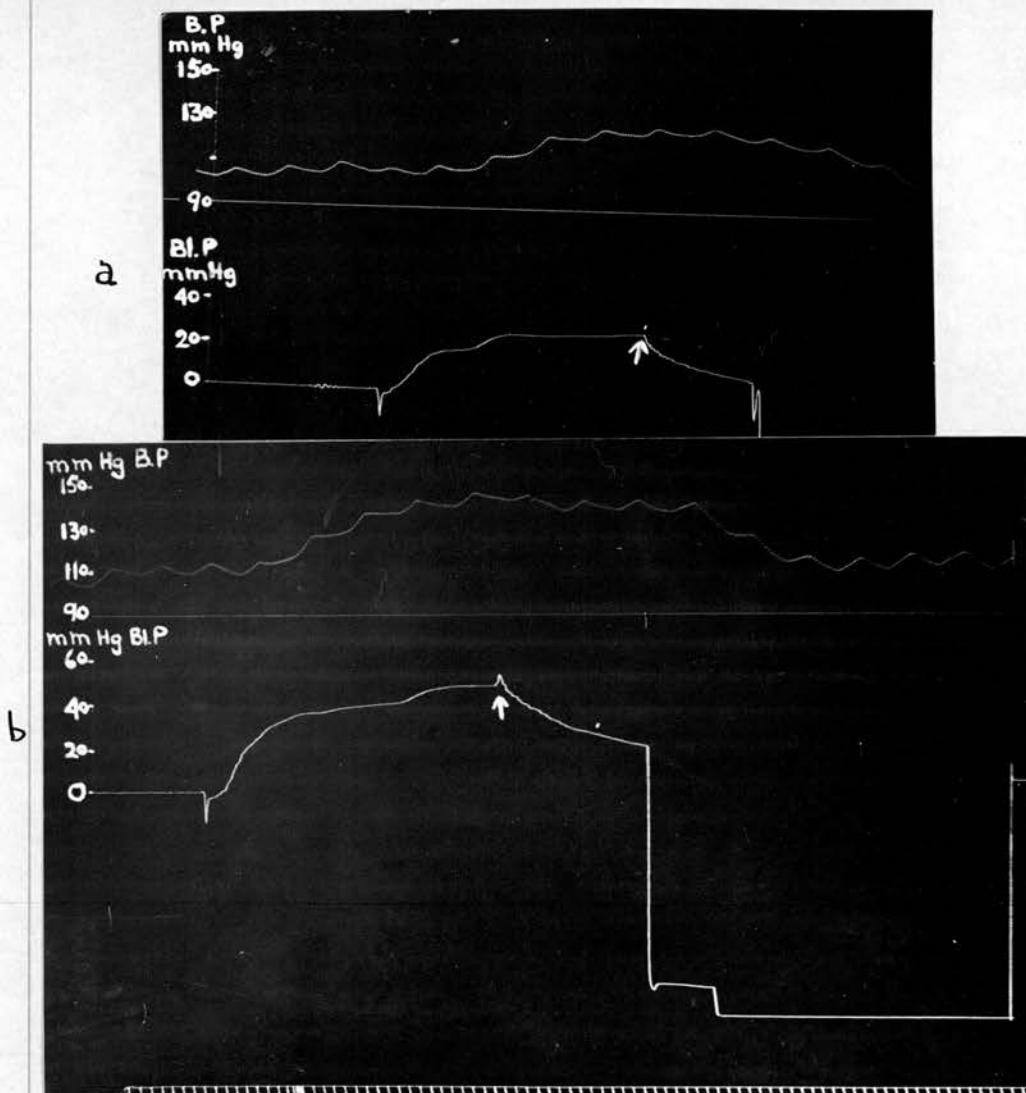


Figure 6

Effect of bladder distension at different pressures, on blood pressure.

(After bilateral vagotomy and carotid sinus denervation.)

B.P. - Blood pressure.

Bl.P. - Bladder pressure.

Arrows indicate - filling stopped.

Time - second.

a Bl. P 22 mm Hg

b Bl. P 50 mm Hg

these conditions too the blood pressure starts to rise after a certain period (lag phase) from the onset of the filling of the bladder. The lag phase varies from 5 - 40 seconds, depending on the rate of filling the bladder. During the filling phase, the rise in blood pressure is more steep and progressive than those found in Group A. No indication of intermittent rise is found. When the filling is stopped and the bladder is kept distended (1) the blood pressure goes on rising if the intravesical pressure still remains the same as that in the filling period, (2) the blood pressure falls slightly if intravesical pressure comes below the level obtained during the filling stage.

Finally, when the bladder is emptied, the blood pressure comes down but usually takes a long time to return to the prefilling level.

When the experiments are repeated, the findings are not always of the same patterns. Usually following emptying, the blood pressure comes down and becomes steady at a lower level progressively, and the responses to subsequent distension get poorer. No depressor effect has yet been obtained.

Group C

In the same animal, when experiments are done before and after bilateral vagotomy and carotid sinus denervation, findings discussed already in Group A and Group B are obtained. Ten experiments

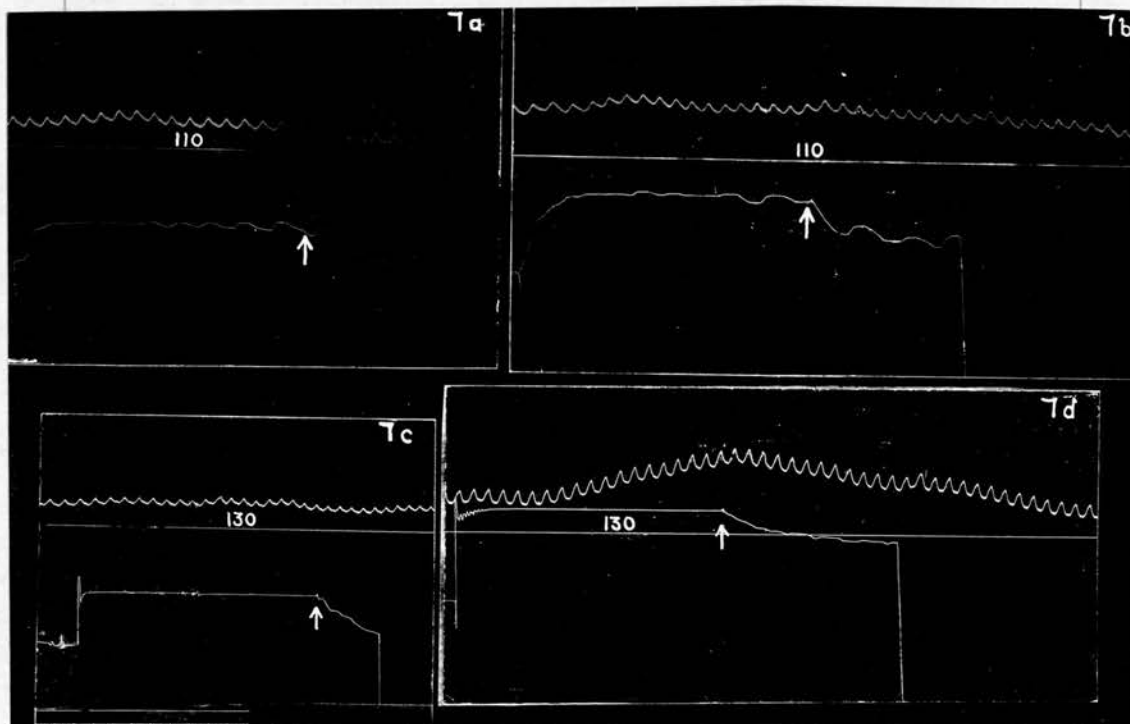


Figure 7

7a and 7b before denervation
 7c and 7d after denervation

Vagal and carotid sinus.

In each upper tracing blood pressure
 a, c - 45 mm.Hg. (bladder pressure)

In each lower tracing bladder pressure.
 b, d - 65 mm.Hg. (bladder pressure)

Note: In 7d, blood pressure falls as
 filling is stopped and intravesical
 pressure comes down (vide Figure 6).

Time 5 seconds.

Arrows indicate filling stopped.

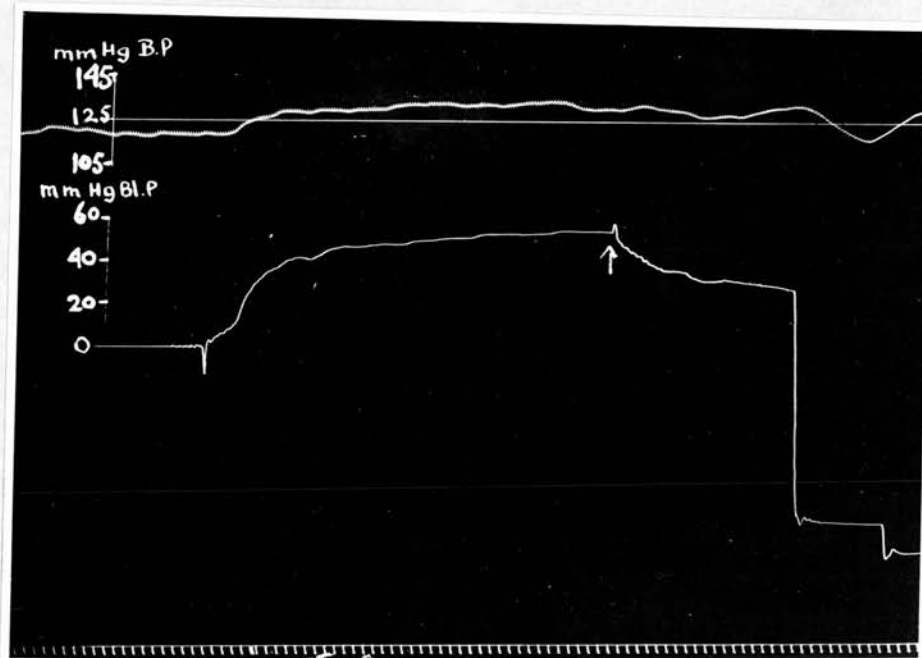


Figure 8 α

Effect of bladder distension on blood pressure.
(Before vagotomy and carotid sinus denervation.)

B.P. - Blood pressure.

Bl.P. - Bladder pressure.

Arrows indicate - filling stopped.

Time - second.

(Cf Fig 8b)

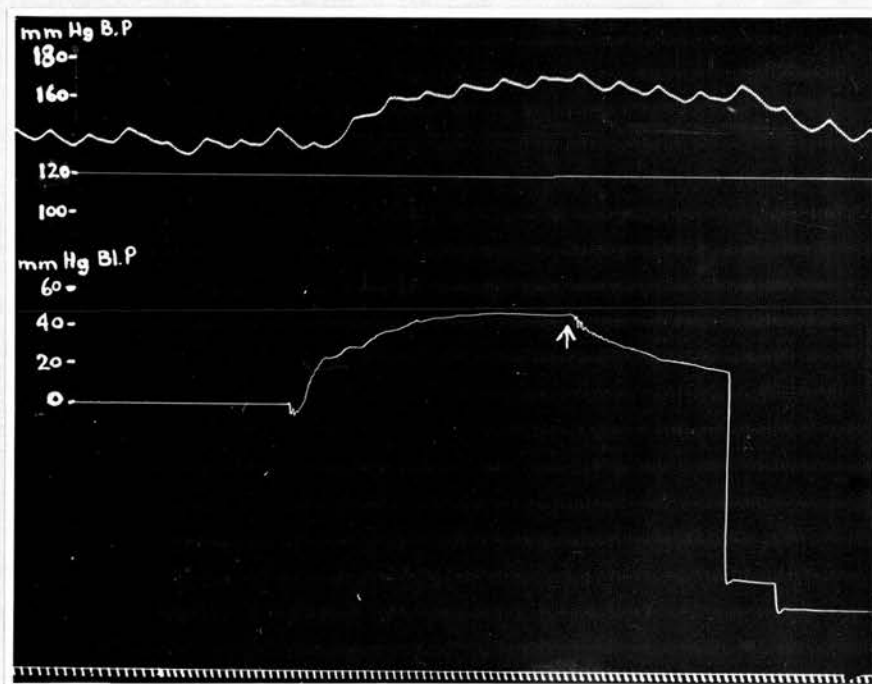


Figure 8b

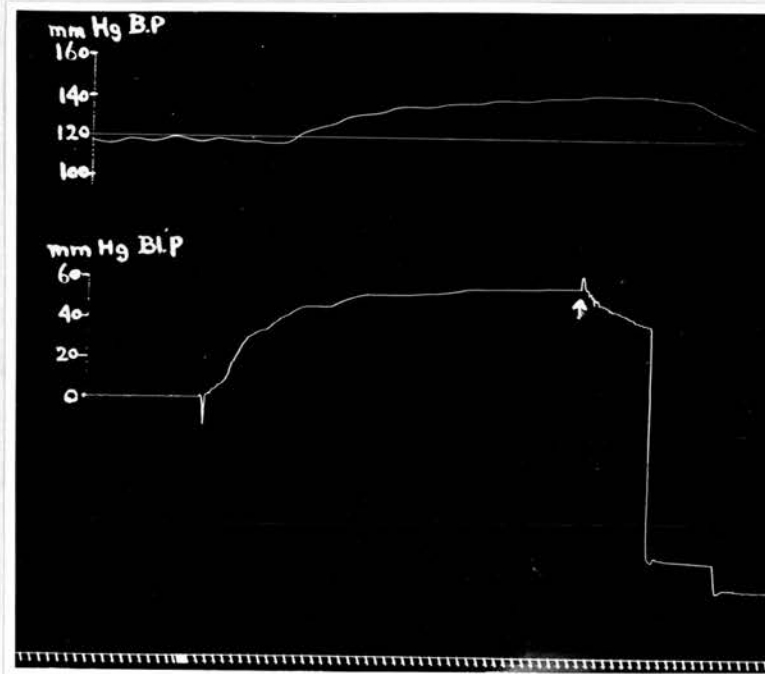
Effect of bladder distension on blood pressure in the same animal (vide previous picture), after bilateral vagotomy and carotid sinus denervation.

B.P. - Blood pressure.

Bl.P. - Bladder pressure.

Time - second.

a



b

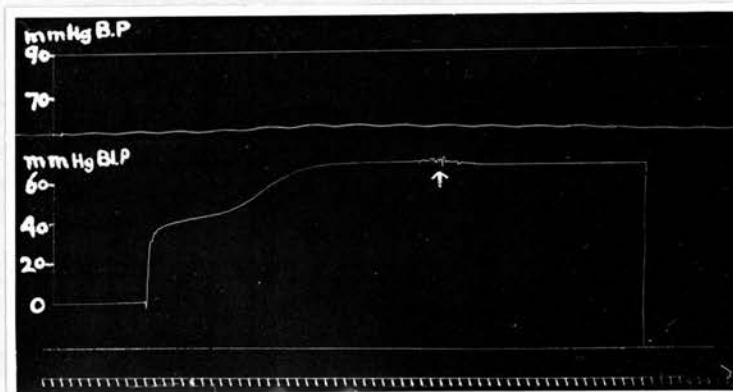


Figure 9

Effect of bladder distension on blood pressure

(a) before splanchnicectomy

(b) after splanchnicectomy.

Arrows indicate - filling stopped.

Time - second.

To note

a - after bilateral vagotomy and Carotid Sinus Denervation
(vide Figs 8 a, b)

b - no rise in B.P.

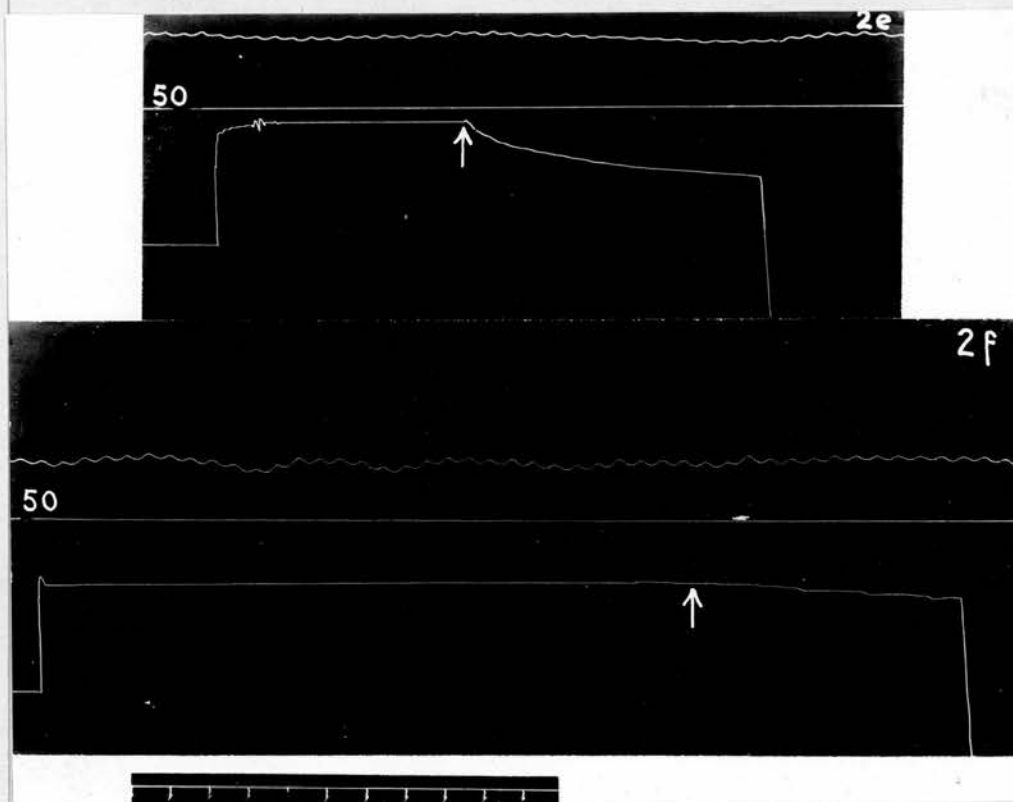


Figure 10

2e, 2f Upper tracing blood pressure.
 Lower tracing bladder pressure.
 Time 5 seconds.
 Arrows indicate filling stopped.
 (Cf. Figs 2, 2a)

(After bilateral splanchicectomy)

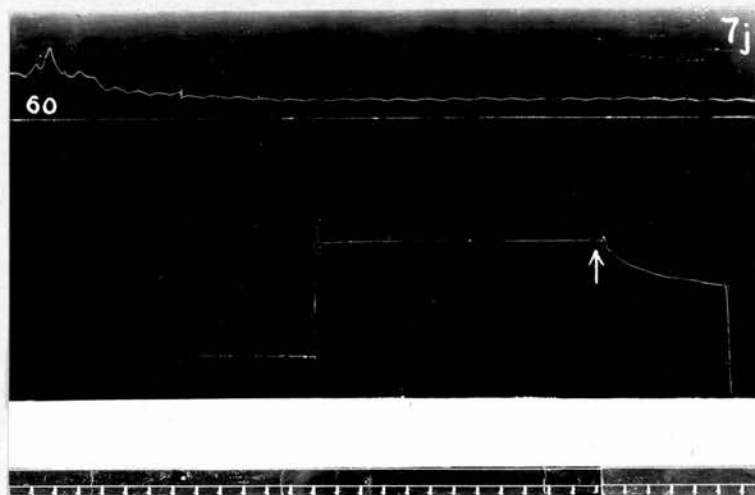


Figure 11

Upper tracing blood pressure.

Lower tracing bladder pressure.

Time 5 seconds.

Arrows indicate filling stopped.

(4. 34.7)

After bilateral Splanchnicectomy

have been done, and in each one similar results have been obtained. Figs. 7 and 8 show the results.

Group D

All the ten experiments in Group C were terminated by doing bilateral splanchnicectomies and repeating the procedure of distending the urinary bladder, to see if the rise in blood pressure can still be obtained. Figs. 9, 10 and 11 show the results. The reflex response is abolished.

Group E

Considering that the pressor response may be poor if the resting blood pressure is high (before filling of the bladder is commenced), some experiments were planned.

Before vagotomy and carotid sinus denervation, when the blood pressure remains high above 150, the pressor response is poor. Following denervation, the pressor response appears to be slightly greater, but not so marked a difference is obtained as seen previously in Group C.

Group F

Following the denervation in these acute experiments, it was found that the blood pressure usually comes down to a level 20 - 30 mm. higher than before denervation. Usually it takes $\frac{3}{4}$ to 1 hour to reach this level. Out of curiosity, it

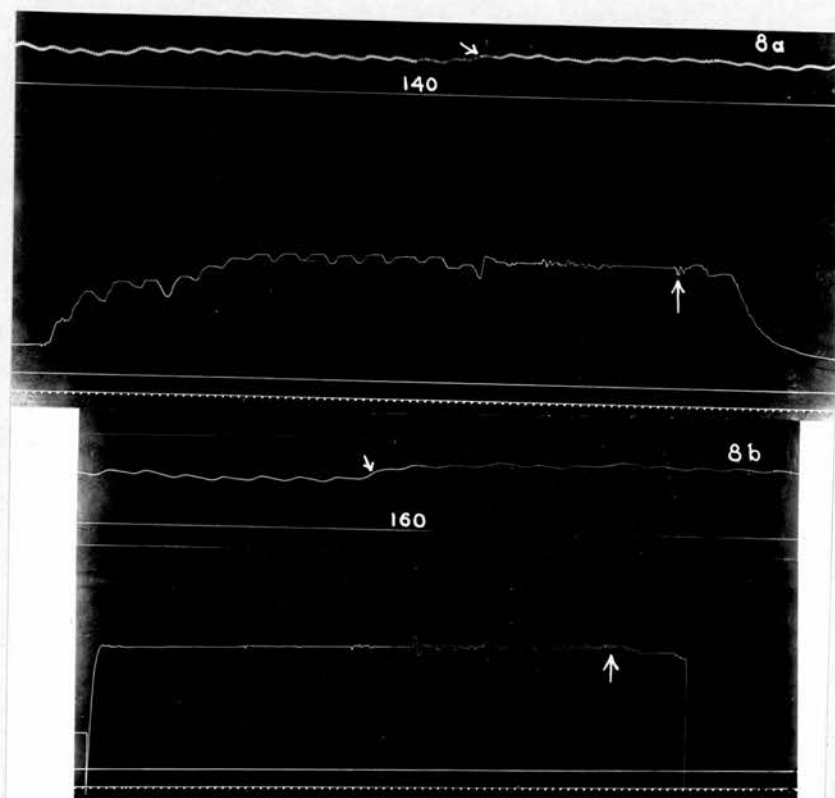


Figure 12

Upper tracing blood pressure.
Lower tracing bladder pressure.

8a Before denervation. (Vagal and Carotid Sinus)
8b After denervation. " " "

Arrows above indicate change
in level of pressure.

Arrows below indicate filling
stopped.

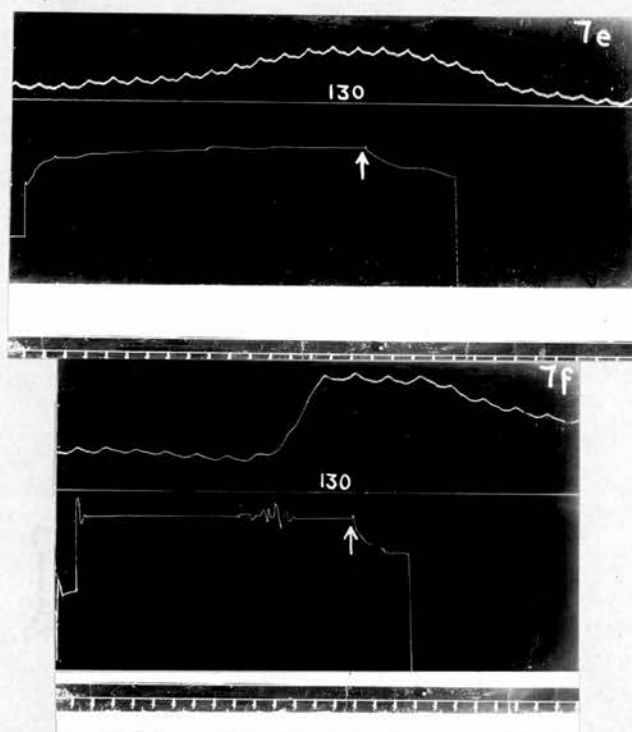
(Time Sec.)

was decided to find out how satisfactory the pressor response almost immediately after denervation can be or whether there may be a fall of blood pressure at this heightened tone of vasomotor system. The results are shown in Fig. 12. It is evident that at these stages the responses are poor and still a pressor response is obtained.

Group G

In some animals, following vagotomy and carotid sinus denervation, when the bladder is repeatedly filled and emptied, a similar pattern of blood pressure curves are usually obtained as that described before. But the height of the rise of blood pressure (% increase of the original) gets less. If now the bladder is filled at a quicker rate than that used before, even keeping the same pressure head, either blood pressure rises to the same extent or more. Sometimes the patterns look like adrenaline pressure curves (Figs. 13, 14 and 15).

Comparing Figs. 7 and 13, 14 and 15 (as these are of the same animal), it will be evident also that, as the rate of filling the bladder is increased, the lag phase is reduced. Interpreting the lag period as the minimal volume of fluid necessary to distend or stretch the bladder "adequately", as the term was used by Sherrington (1906), it appears that about 25 - 35 ml. of fluid are the optimal amounts.



Figures 13, 14

In each upper tracing blood pressure.
lower tracing bladder pressure.

Time 5 seconds.

7e 65 mm.Hg. pressure head -
rate of filling 60 ml./minute.

7f 65 mm.Hg. pressure head -
rate of filling 90 ml./minute.

Arrow indicates filling stopped.

After bilateral vagotomy and Carotid Sinus
Denervation (vide Fig 7).

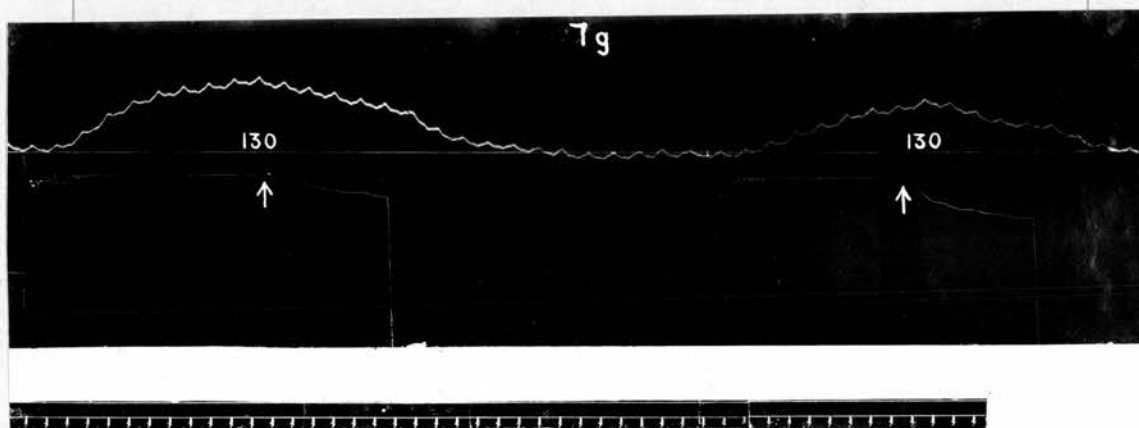


Figure 15

Upper tracing blood pressure.
Lower tracing bladder pressure.

7g shows repetition of experiments
using same pressure head and
same rate of filling. (Rate
of filling 120 ml./minute.)

Time 5 seconds.

Arrow indicates filling stopped.

Group H

To prove finally that the stimuli causing rise in blood pressure are arising within the bladder, five experiments were done, in each of which the bladder was brought out and the filling started. Responses (rise in blood pressure) obtained are similar to those described previously (Fig. 16).

Such procedures were not followed in each case because it was found that, when the bladder is kept outside for a long time (15-30 mins.), the bladder shrinks to a hard, tense, nutmeg form. Why, it is difficult to say. It is almost impossible to carry on further distension with these dead "tombs" of bladder. Keeping the bladder covered with a moist gauze rung in warm (N) saline, does not prevent the bladder getting tense and hard.

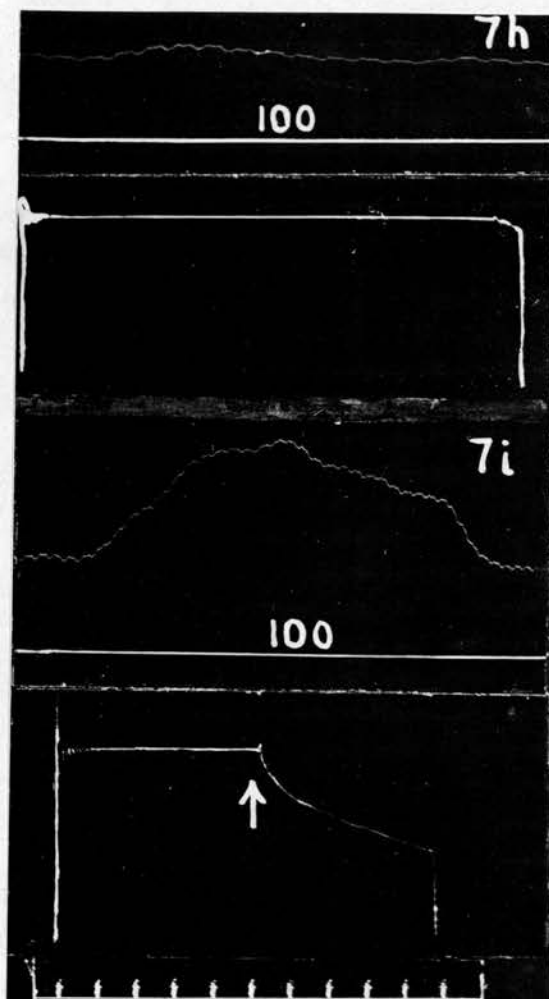


Figure 16

In each 7h, 7i upper tracing blood pressure.
lower tracing bladder pressure.

Time (5 seconds)

7h 45 mm.Hg. pressure head, 90 ml./minute.

7i 60 mm.Hg. pressure head, 90 ml./minute.

Arrow indicates filling stopped.

DISCUSSION

Rosenblueth and Schwartz (1935) investigated the role of different anaesthetics on cardiovascular and vasomotor reflexes. They found that such reflexes can be readily elicited when chloralose is used as an anaesthetic. This was further confirmed later by Pinkston, Partington and Rosenblueth (1936).

Watkins (1938) used various anaesthetics, and remarked that there was no difference in their effects on reflex vasomotor responses. Downman, Goggio, McSwiney and Young (1943-44), after using various anaesthetics, reported that chloralose is not a suitable one in experiments to demonstrate viscerovascular reflexes. But the results obtained in the present investigations indicate that under chloralose anaesthesia (with the dosage described), viscerovascular reflexes, as judged by their effect on blood pressure, can be satisfactorily elicited.

When the urinary bladder is distended, the blood pressure rises. This is in agreement with the finding of Watkins (1938) that distension of the urinary bladder causes a pressor response.

The duration of the lag phase in the present series of observations has varied from 2 - 40 seconds. In the series reported by Watkins, it was 2 - 5 seconds. The difference in findings is probably due to the fact that Watkins used a very quick rate of distension and a higher pressure

head as well.

At the same pressure head, when the filling of the bladder is continued, the blood pressure rises progressively. No attempt has been made to correlate in each experiment the increase in volume or capacity of the bladder with the percentage increase in blood pressure, but it was evident from the results of two experiments that, following the lag phase, such correlation tends to be a linear slope. This is strongly suggestive of the fact that stretch receptors are situated in the bladder wall in such a way that more and more of them are stimulated as the bladder is distended. Schumacher and Guthrie (1951) have also reported similar observations in paraplegics. They found repeatedly that increasing the fluid volume led to further increase in reflex effects, though the ultimate intravesical pressure was not increased and even sometimes diminished. The present observations differ only in that if intravesical pressure becomes less, the blood pressure does not rise any more (Fig. 7). Such a picture will also be seen in the acute spinal cat. That the volume of the bladder, the intravesical pressure remaining constant, can influence the reflex responses, is explicable on Laplace's law. It states that for a hollow sphere $P = \frac{2T}{r}$ where P is internal pressure (excess over external pressure), T is tangential tension in the wall, and r is the

radius. For a cylinder, the formula is $P = \frac{T}{r}$. Now, as the bladder is filled, the radius increases. So, P remaining constant, T will vary directly with r. But to interpret the percentage of changes in blood pressure with the volume of the bladder, one has to determine the simultaneous fluctuations in the postural adaptability of the bladder smooth muscle. This is a complex problem as evident from the graph (Watkins, 1938) showing the ranges of blood pressure changes in relation to bladder volume.

Evidently, this progressive rise of blood pressure with the continuous filling of the bladder at the same pressure head may be one of the reasons for the marked variations in the amount of rise of blood pressure shown by Watkins in the curve (depicting relationship of bladder pressure to rise in blood pressure).

But it has also been shown that, when a lower pressure head, i.e. 45 mm.Hg. or less is used in filling the bladder, the reflex response shown by a rise in blood pressure is poor, both before and after vagotomy and carotid sinus denervation. But with increasing pressure, the response becomes more and more marked. This observation suggests that the reflex vasomotor response is primarily dependent on the intravesical pressure. This is in agreement with that reported by Watkins (1938) in nonspinal preparations, and also with that reported by Guttmann and Whitteridge (1947) in spinal men.

During the phase of distension, when no more fluid enters the bladder, the intravesical pressure does not always remain at the same level as that in the filling phase. In those cases, where the intravesical pressure falls below the previous level, the blood pressure starts falling. If the intravesical pressure remains at the same level, the blood pressure goes on rising. This was always seen following vagotomy and carotid sinus denervation.

These findings suggest strongly that effective impulses arising from the bladder wall depend essentially on its degree of stretching and distortion of the end organs. Though it is a function primarily of intravesical pressure, it can also be considerably influenced by the degree of relaxation of the bladder wall. It appears that the stretch of the bladder wall rather than absolute pressure is the effective stimulus. This is emphasised to point out in particular that even in normal circumstances, when the bladder gets full slowly and gradually, there is a progressive increase in the intravesical tension and stretch because of the limited capacity of the relaxation of the bladder wall. That even a pressure of 50 mm.Hg. can be obtained under normal conditions has been observed (Brian More, from Whitteridge, 1954). It is quite logical to believe then in hypertonic bladder due to organic or functional

changes in the bladder wall with disease or old age, or following spinal cord lesions, even a small distension can precipitate reflex vasomotor effects (as compared with a healthy normal one). This probably explains why vasomotor disturbances are found in "dumping syndrome" following partial gastrectomy. A small stomach does not retain the food - it passes out through the stoma quickly and the jejunum is suddenly stretched. That the reflex vasomotor reactions can be very marked is evident when one is not allowed to urinate or defaecate or vomit when there is an uncontrollable desire to do so.

That adequate distension is the effective stimulus for eliciting the viscerovascular reflexes was first stressed by Sherrington (1906). He considered that pain and other reflex responses obtained in cases of acute biliary or ureteric colic are obtainable when the parts behind the occlusion dilate and are stretched. Clinical observations on these cases of colicky pain illustrate also how the symptoms and signs of acute illness disappear when the little stones causing obstruction in the passages of biliary duct or ureter become suddenly loose, and the continuity of the lumen is restored.

When the bladder is emptied, the blood pressure comes down to the prefilling level, sometimes quickly, sometimes slowly. This again proves that viscerovascular reflexes are caused by

the distension-stretching of the hollow viscus lined by smooth muscles. No attempt has been made in the present series to see the effects of distension of de-afferented bladder on the blood pressure. But the observations made by Talaat (1937), Watkins (1938), and Thompson and Witham (1948) indicate that such afferents travel by both the hypogastric and the pelvic splanchnic nerves. The individual role of these two sets of nerves is difficult to assess on a general platform, because of the species differences studied.

The important and interesting observations in the present series have been that (i) the rise in blood pressure is much more marked following vagotomy and carotid sinus denervation, and (ii) such reflex response is abolished following bilateral splanchnicectomy.

The absence of reflex vasomotor response following splanchnicectomy proves the suggestion of Whitteridge and his colleagues that rise in blood pressure following the distension of bladder is due to splanchnic vasoconstriction. Even if any other peripheral vascular bed takes part simultaneously in the increase of peripheral resistance, its contribution is not of any marked significance in the cat.

When vagi and carotid sinus nerves are intact, the rise of blood pressure is not so pronounced, probably because as the splanchnic vascular bed

undergoes constriction, the increased peripheral resistance causes a rise in blood pressure and immediately impulses are sent up from baroreceptors by vagi and carotid sinus nerves to the suprasegmental vasomotor centre, which in turn controls the spinal neurones (in the path of splanchnic vasomotor centre) by inhibitory influence. Therefore, the response shown by the rise in blood pressure remains poor. That the rise of blood pressure is not always a steep slope but in more occasions an interrupted one while the bladder is being filled, is further in support of the explanation given just before. It may also be due to compensatory vasodilatation in other peripheral vascular beds, thus counteracting the effects of splanchnic vasoconstriction.

But when the vagi are cut, carotid sinuses are denervated, the afferent arc to the suprasegmental vasomotor centre from baroreceptors in arch of aorta or carotid sinus not functioning, and therefore check influence from it to spinal vasomotor centre over splanchnic vascular bed is no longer active, and therefore the reflex responses shewn by rise of blood pressure become more brisk. Whether due to the release of the suprasegmental inhibitory influence, the spinal centres assume autonomicity and increased excitatory state, or the excitatory influence sent by suprasegmental centre gains upperhand, cannot be ascertained from the

results obtained in nonspinal preparations. But it has been shewn that viscerovascular reflexes can be obtained in spinal preparations as well (Sherrington, 1899; McSwiney et al., 1947; Guttman and Whitteridge, 1947). Later on, evidence will be given that viscerovascular reflexes can also be elicited satisfactorily in acute spinal preparations.

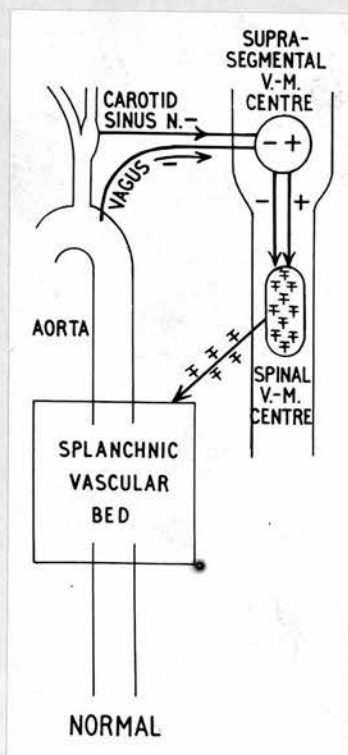
Re-analysing Sherrington's work (1906), it will be evident that, in order to produce a rise in blood pressure in the chronic spinal cat, he cut the vagi. The experimental conditions in which he obtained the reflex vasomotor responses are not strictly comparable to the nonspinals with vagotomy and carotid sinus denervation. But it may be drawn on an analogy that in his case, as the vagi were cut, the suprasegmental control was absent. In the present series, vagi are cut and carotid sinuses are also denervated.

Bayliss and Bradford (1894) found on stimulation of 11th, 12th, 13th dorsal nerves (peripheral ends of both anterior and posterior roots together) that the vasomotor response is characterised by the increase in blood pressure. Simultaneously there were evidences of vasoconstriction in visceral beds and muscle beds of the extremities. The vagi and carotid sinus nerves were intact.

The same roots (used by Bayliss and Bradford, 1894) contribute to the splanchnic nerves also.

The present observations have also shewn that the reflex rise in blood pressure following distension of the urinary bladder is abolished following bilateral splanchnicectomies.

It is, therefore, difficult to believe that before vagotomy and carotid sinus denervation, the less marked rise in blood pressure in the present series can be due to compensatory vasodilatation in other parts of the body. It is more likely that in viscerovasomotor reflexes, where splanchnic vasoconstriction is the predominant mechanism in the rise of blood pressure, the intact vagi and carotid sinus nerves have a considerable role in homeostasis. The interrelationship of these mechanisms is shewn in the following diagram.



On the basis of this mechanism, it is possible to explain why McSwiney et al could not elicit viscerovascular reflexes satisfactorily in non-spinal preparations (where vagi and sinus nerves were intact), and suggested a spinal preparation as a suitable one.

The explanation put forth above fits in well to explain also the discrepancy in the findings of Robertson and Wolff (1951) from those reported by Guttman and Whitteridge (1947). Robertson and Wolff (1951) used healthy, normal individuals and, therefore, in presence of "check" nerves, distension of rectum could not produce a well marked rise in blood pressure. In the chronic spinal subjects, the efferent arc of this inhibitory influence will be absent if the lesion is above the level of the origin of the splanchnic nerves. It is also quite logical to believe then that in the series reported by Guttman and Whitteridge (1947) the rise in blood pressure was always much more when the lesion extended higher and higher up the cord, because in a higher lesion the effects of absence of inhibitory fibres will be more evident. Recently, Pollock and Finkelman (1954) have reported that in paraplegics (cervical lesions) there is always a marked rise in blood pressure when an enemata is administered. This evidence supports the conception based on the present experimental findings^{and those} of Guttman and Whitteridge (1947).

Schrager and Ivy (1938) reported that in dogs distension of the gall bladder or common bile duct did not always produce any marked change in blood pressure. Following experimental obstruction of intestine, no definite evidence of rise in blood pressure has been reported yet.

However, all these can be explained on the basis of the present findings and the explanation suggested as ^amodus operandi. When vagi and carotid sinus nerves are intact, splanchnic vasoconstriction produced by the distension of gall bladder or common bile duct or gut cannot be sufficiently pronounced and maintained to cause always appreciable rise in blood pressure.

However, this explanation put forward requires further direct proof that suprasegmental vasomotor centre is exercising normally an inhibitory influence over the splanchnic vasomotor centre. That it does so will be discussed when the results of Chapter 2 are presented. It should be pointed out that under certain conditions it is not possible to reproduce experimentally these reflex vasomotor responses. The constant and most important condition in which it is difficult is when the level of resting blood pressure is already high. It must have been observed in the past by other experimental investigators that it is difficult to elicit a pressure response satisfactorily, if the blood pressure is already high. But there is no such

report in the literature except by Bruce, Martin and Smirk (1944-45) who found that rise of blood pressure by cold pressor test is much less in hypertensives when already the blood pressure is at a high level.

The participation of the splanchnic vascular bed in the redistribution of blood in the body by altering the blood pressure was emphasised by Cushing (1900-01) in his experiments on the mechanism of rise of blood pressure in increased intracranial tension. Barcroft (1925) stressed the importance of the role played by splanchnic vascular bed in the homeostasis of circulation with regard to blood volume. The present investigations add further evidence that in reflex circulatory mechanisms, particularly when hollow viscera are distended, the splanchnic vascular beds are of considerable importance as, by narrowing the splanchnic vessels, varying effects on circulation may be precipitated.

CHAPTER II

By a plethysmographic technique, renal blood flow was first measured (Brodie and Russell, 1905). Since then, various other methods have been used to study changes in renal blood flow. A critical analysis of these methods shows that all the principles used in measuring blood flow through any other vascular part of the body are applicable in the renal blood flow measurement. This is so because each kidney receives only one artery and only one vein drains the blood away from it. Urea clearance and PAH methods of measuring renal blood flow are based on Fick's principles (Rhoads, Van Slyke, Hiller and Alving, 1934; Smith, Rovenstine, Goldring, Chasis and Ranges, 1939). These indirect methods require catheterization of the renal vein without interrupting its flow at the same time. The serious drawback in using these techniques for acute or shortlasting experiments is that these cannot be repeated quickly and, therefore, it is not possible to study changes in renal blood flow for the present investigations. On similar reasonings, the gas diffusion technique introduced recently by Conn, Jr., Anderson and Arena (1952-53) cannot be used for shortlasting experiments.

The technique used by some to measure renal blood flow on the principles of venturimeter (Livingstone, 1925) is most unsuitable as it

involves intra-abdominal manipulations, and the preparation cannot be considered as a physiological one. The other direct methods include (i) diverting the blood flow from renal vein into external jugular by a siliconized or heparinised tube, and to measure the amount flowing per minute by temporarily occluding the external jugular (Selkurt, 1946); (ii) recording the rate of flow in the renal vein by temporarily occluding it near its opening into the inferior vena cava and collecting the blood via testicular or ovarian vein (Keele and Slome, 1944); (iii) by applying thermomuhur or modifications of it on the renal artery or renal vein (Herrick, Essex and Baldes, 1932; Handovsky and Samaan, 1937). All these methods necessitate dissection in the renal pedicle to free the vessels from the perivascular tissue. These procedures necessarily disturb the normal relations of nerves and vessels in the renal pedicle. Moreover, the exposure and manipulation of these vessels are not very simple experimental procedures. Though the left kidney in all species has a longer pedicle than the right one, it is a fact that the pedicles are not long enough always to allow sufficient space for the necessary technical adjustments. This is particularly true for small animals like rabbits or cats. The renal veins in particular are extremely fragile in these small animals. Recently, electromagnetic

flowmeters have also been used in the measurement of renal blood flow (Spencer, Denison and Green, 1954), but the technical difficulties encountered in this method remain the same as described above.

In the face of these difficulties, studies on renal blood flow have been more qualitative at present. Cineangiography(Barclay, Daniel, Franklin, Prichard and Trueta, 1946) and ultra-violet microscopy (Mukherjee, 1952; Mukherjee, Simpson, Smith, unpublished) are used for these purposes. The latter one gives only a good idea whether the blood is flowing or not at the spot or spots on the surface of the kidney, that are being observed. Cineangiography, when properly done, gives more valuable information. Though the pictures do not in themselves give any idea about the dynamics of the events, considered serially these certainly represent the changes in the renal vascular bed. Attempts to analyse them quantitatively will be hazardous because the pictures are being taken in one plane only, and all the blood vessels within the kidney lying in parallel in that plane will be superimposed on one another and, therefore, it is wiser to interpret them only qualitatively.

In recent years the physiologists have become interested not only to study changes in renal blood flow but also to study the pattern of distribution of blood within the kidney. Cineangio-

graphy is of unique value in this type of work. The other methods used to study intrarenal distribution of blood are by injecting dyes or ink, by injecting P^{32} labelled red cells (Mukherjee, 1952), and then removing the organ and cutting it to see how the test substance is distributed. Of these methods, P^{32} labelled red cell technique is certainly most valuable because it is a physiological mass of the living body (except that it is labelled) and cannot by itself cause any disturbance to the circulation. By removing the kidney and subsequently using Pickworth's stain, the distribution of the blood within the kidney can also be studied.

For the present investigations, however, it is necessary to investigate the changes in renal vascular capacity, renal pulse volumes and renal blood flow. By using the principle of Brodie and Russell (1905), it is possible to study all the three together, but the obstruction of renal vein only is technically difficult and undesirable for the intense renal congestion produced. It is worth remembering in applying this "only venous" occlusion technique in renal blood flow measurement that normally 20-25% of cardiac output flows through the renal vascular bed per minute.

Mann and his colleagues have used plethysmography and thermostromuhr simultaneously in measuring renal blood flow. They have found that

whenever there is renal vasoconstriction, thermomuhur readings showed a considerable reduction in renal blood flow (Herrick, Essex and Baldes, 1932). On physical laws, it is true that vasoconstriction is not necessarily followed by reduced blood flow. If the blood pressure gets simultaneously very high, the increased pressure head can overcome the increased resistance and the blood flow may remain the same or even increase. But if the same vascular bed participates in vasoconstriction causing increase in peripheral resistance and rise in blood pressure, and if the vasoconstriction persists during the phase when blood pressure is increased, and if the pulse volume gets simultaneously decreased, the evidences are reliable proofs of "reduced blood flow" through the same vascular bed. In the present investigations, changes in the renal volume and the amplitude of the renal pulses have only been studied. Actual measurement of renal blood flow on the principle of venous occlusion technique used in limb or finger plethysmographic studies necessary for more precise data will be undertaken in future.

Method used

On the principles discussed above, it was decided to use plethysmography technique. An "egg-cosy" method has been used. These are ordinary Easter egg plastic containers made in two parts,

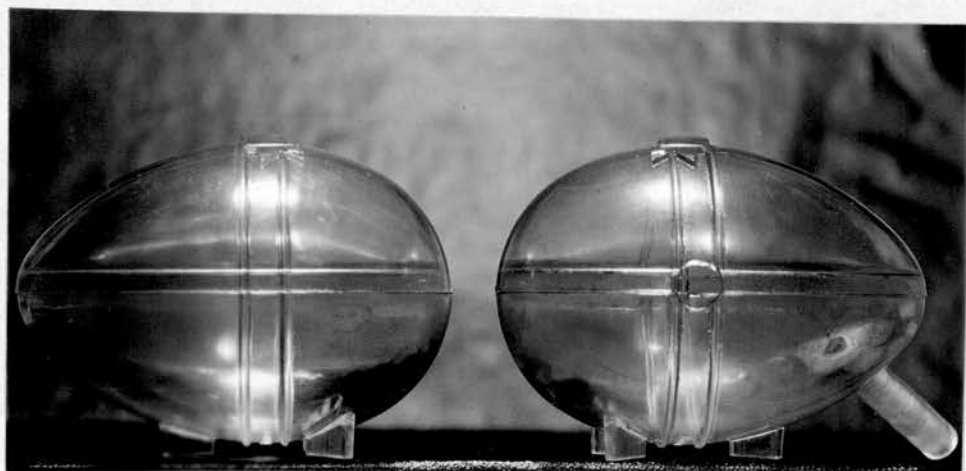


Figure 1

Plethysmograph.

which can be obtained in various sizes (Fig. 1).

A side hole is bored in the cosy through one of its leaves, usually near the end, and a small hard perspex tube hollow in the centre fixed into it permanently. The perspex tube is 2.5 cm. long, 0.5 cm. wide, and the calibre of the lumen inside has a diameter of 2 mm. It is fixed to the leaf in such a way that it is partly projecting within the plethysmograph (only 3-5 mm.). It is done so because a few drops of chloroform now put round the margins of the opening in the leaf fix the perspex tube to the plastic surface of the leaf. The tube now becomes an undetachable part of the plethysmograph.

The one used in the present series has a capacity of 56 ml. At the middle of one side a hole 6 mm. diameter is made. The margins are lined with vaseline, and the left kidney^{is}/exposed extraperitoneally, cleared from the perinephric fat, and is put into the cosy. The hilum of the kidney fits into this hole. The perihilar fat acts as a cushion to make this hole air tight, and no further sealing is necessary. The only precaution to be taken is to adjust the position of the cosy so that the pedicle is not kinked.

The whole set-up is shown in the diagram. The renal pulse volume and changes in the renal vascular capacity are then recorded optically by the use of a membrane manometer, one single hard



plastic tube connexion being used between the manometer and the plethysmograph. This is much better than thickwalled rubber tubes or lead tubes. The sensitivity of the membrane is such that 0.1 ml. added air displaces the beam 3 - 4 cm. at the camera, this displacement being within the linear range of the membrane.

A muscle splitting incision (like McBurneys) has been preferred to expose the kidney in the left loin. This is of advantage because the opening made by splitting muscles in the lateral abdominal wall prevents any undue bulging out of peritoneum and the viscera due to respiratory movements.

Results

Fifteen experiments have been done. In five only, the changes in renal vascular bed were observed before and after vagotomy and carotid sinus denervation in each same animal. The results of one experiment are shown in Figs. 2 and 3.

In ten animals, following denervation, changes in renal vascular bed were observed by repeating the distension of bladder at different rates but keeping the pressure head the same. The results are shewn in Fig. 4.

In each experiment the results of splanchnic-

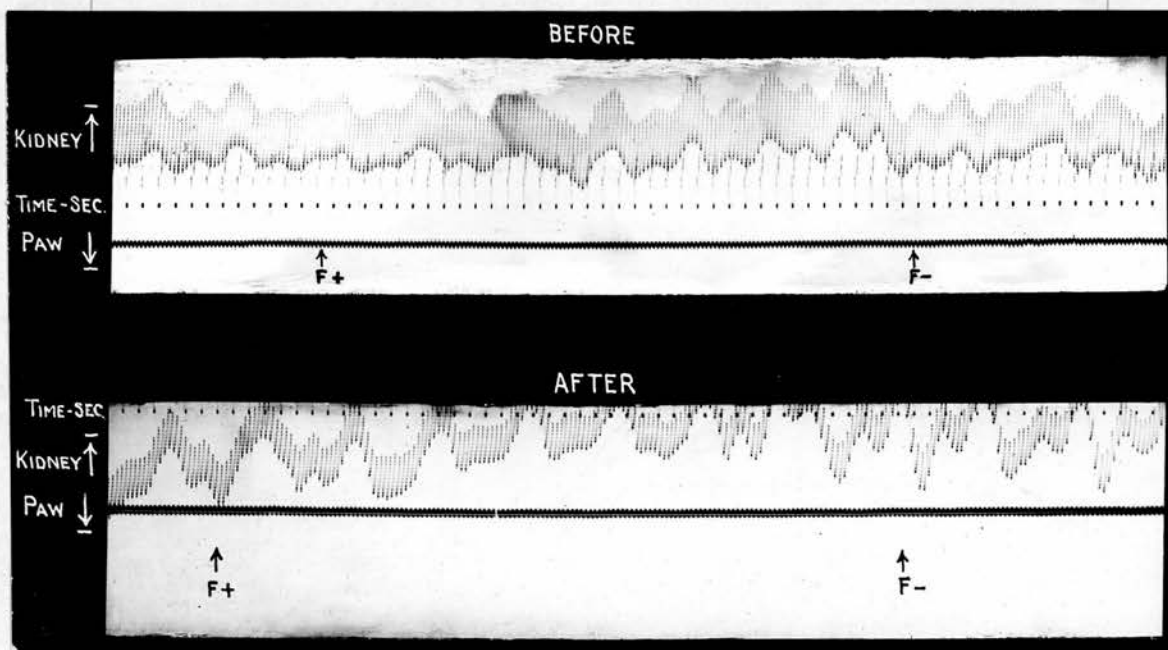


Figure 2

Before and after vagotomy and
carotid sinus denervation.

F + Bladder filling starts.

F - Bladder filling stopped.

↑ ↓ indicates decrease in volume

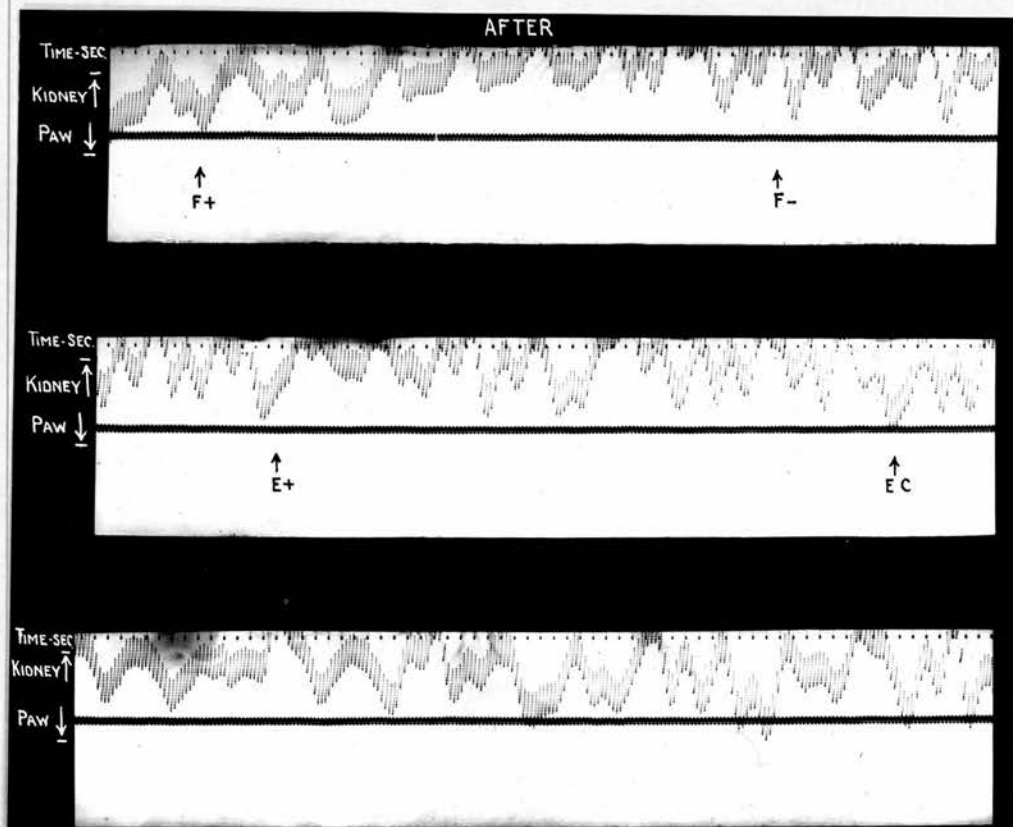


Figure 3
vagotomy and Carotid Sinus

After denervation - complete run.

F + (Bladder) Filling starts

F - Filling stopped

E + Emptying starts

E - Emptying complete

(E +) - (F -) Distended bladder.

↑ indicates decrease in volume

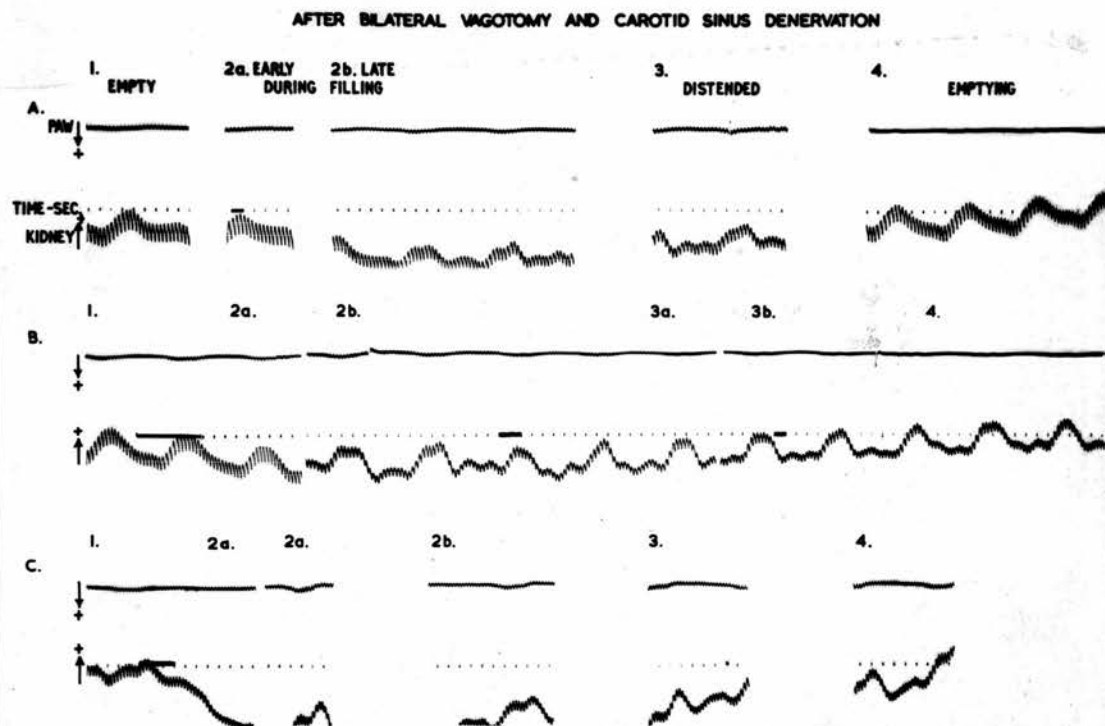


Figure 4

Numericals at top denote stages of bladder;
signals (-) indicate onset of the stage
shewn next.

+
↑, ↓ indicate increase in volume

ectomies were also observed.

For the sake of convenience, the results will be discussed together. First the majority of the findings will be taken for discussion.

A. During the filling phase. Within 2-5 secs., renal vasoconstriction sets in. It is feeble and less marked before denervation. But after denervation it increases and becomes very marked as the filling of the bladder progresses.

As the bladder gets more and more distended, the renal pulses become smaller. The dead space occupied by the plethysmograph and the tube amounts to 71 ml. The volume of the kidney is usually 6-8 ml. Therefore, the changes in the dead space caused by the diminution in the volume of the kidney do not affect the sensitivity of the membrane such that the changes in the size of the pulses can be considered as mechanical in origin. Therefore, the diminution in the renal volume and reduction in the size of the pulses as seen in the present investigations are due to active vasoconstriction. (vide Blood Pressure changes, Ch I)

B. During the stage of distension.

Pre-denervation - There is return to pre-filling stage.

Post-denervation - Vasoconstriction and reduction in renal pulses are not increased any more. On the other hand, the tracings indicate that there is a tendency towards restoration of

prefilling volume of the renal vascular bed and it is alternate with vasoconstriction. Whether this is due to mechanical disturbances from increased intra-abdominal pressure on renal vein or inferior vena cava, will have to be considered. Also other factors may be responsible. These will be discussed later on.

C. Emptying phase. As bladder is emptied, renal vascular volume is restored and sometimes an increase in the volume sets in. But the amplitude of the renal pulses do not always become the same as in the prefilling stage. Therefore, it appears that the evidence of increase in renal volume is not an active one.

Fluctuations in renal volume during distension phase may be due to:-

- (i) Mechanical disturbances, e.g. (a) pressure of full bladder on renal vein directly or by compression of inferior vena cava; (b) increased intra-abdominal pressure due to transmission from intravesical pressure, and its effects of compression on veins.
- (ii) Reflex neurogenic disturbances. (a) Increased intrarenal tension due to rise in blood pressure (Swan, Moore, Montgomery, 1952).
(b) Efferent venular constriction.

If mechanical effects are the cause, these would be present even after splanchnicectomies. It has been found following splanchnicectomy that an

BEFORE AND AFTER SPLANCHNICECTOMY

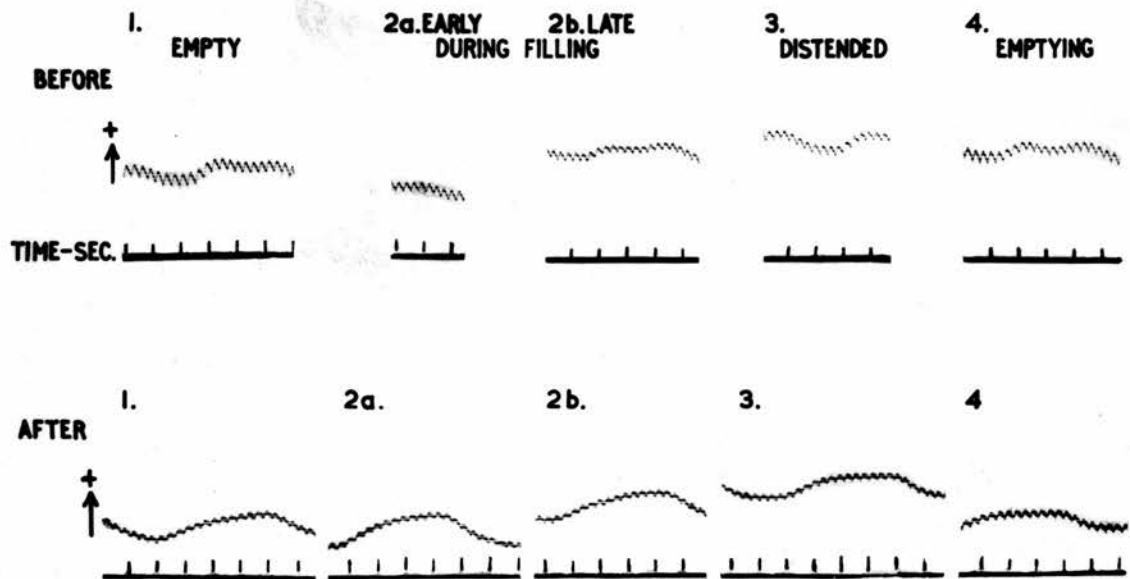


Figure 5

Numericals at top denote stages of bladder, as in Figure 4.

+ indicates increase in volume

increase in renal volume can still be obtained. Therefore, these are due to mechanical causes (Fig. 5). Linzell (1950) found that spontaneous volume changes in the mammary gland were due to similar mechanical disturbances caused by distended bladder pressing on the inferior vena cava.

But the increased volume of renal vascular bed following complete emptying of bladder cannot be explained on mechanical causes. Following splachnicectomies, these are not obtained. Whether such changes are due to delayed effects of small amounts of adrenaline in circulation or nervous reflexes which produce constriction of efferent vessels has to be considered.

In the previous chapter, it was shewn that sometimes the patterns of changes in blood pressure following distension of urinary bladder look like typical adrenaline blood pressure curves. Efferent arteriolar constriction appears the most likely mechanism. This is because, in order to build up sufficient intraglomerular pressure for filtration, it is necessary that efferent arteriolar constriction should overlast afferent one. But whether this happens or not has to be verified by experiments in future.

Following splachnicectomy, occasionally increase in renal volume during the terminal stages of filling of the bladder or during distension stage are observed.

Attempts were made in five experiments only to study changes in paw volume, if any, during the filling and distension of the bladder.

The method used here is the same as used by Whitteridge and his colleagues for finger blood flow measurements (Guttmann and Whitteridge, 1947). In two animals, left forelimb was used and in the rest the hindlimb. Results are shown in Figs. 2, 3 and 4.

No consistent change was found except occasionally feeble attempts at vasoconstriction. The lack of findings may be perhaps because the sensitivity of membrane used was not so much as reported by Downman, Goggio, McSwiney and Young (1943-44). In the present series for the paw volume changes, the sensitivity of the membranes was such that 0.1 of air added displaced the beam 3 cm. at the camera, displacement being within the linear range of the membrane.

Discussion

In Chapter 1 it has been shown that the blood pressure rises when the urinary bladder is distended, and this response is abolished following bilateral splanchnicectomy. The findings in this chapter give additional evidence of splanchnic vasoconstriction (in the renal vascular bed) following urinary bladder distension. This is not seen following splanchnicectomy. In Chapter 1, the

findings indicated that the intact vagi and sinus nerves exercise an inhibitory control over the splanchnic vasomotor mechanism. The changes in renal circulation before and after denervation, as shewn in this chapter, confirm the previous findings.

Diminution in renal volume and reduced renal pulses usually indicate reduced renal blood flow. But without measuring the changes in renal blood flow, no definite statement can be made as to how much the flow is reduced. Twenty per cent of the cardiac output passes through the renal vascular bed per minute. The active role of the kidneys in the homeostasis of redistribution of blood in the body is now widely recognised (Van Slyke, 1951-52). But the factors influencing the blood flow within the kidney are many and, when the exhaustive literature on this subject is analysed critically, it does not permit any worker in this field to explain satisfactorily the disturbances in renal circulation in various conditions on any definite, solitary premise. The anatomical details of the vascular architecture within the kidney are still inadequately known. In addition, the recent contributions of various investigators to the knowledge of this part have caused more confusions because of different findings. As our interest for the present lies only in finding out the changes in renal vascular bed, we omit these

discussions on incongruent findings.

Reflex anuria due to calculus in one ureter has been recognised clinically for a long time. Urological surgeons are now of unanimous opinion that removal of the calculus is the ideal treatment. The evidences presented in this chapter indicate that reduction in renal blood flow can certainly be of reflex origin and, therefore, removal of the ureteral calculus and thus relieving the obstruction are rational. During cystoscopy and trans-urethral fulgration or diathermy of the prostate, it is necessary to keep urinary bladder distended. Post-operative anurias have been reported occasionally. It is worth while investigating into such cases whether these are of reflex origin. Reflex renal vasoconstriction can be from various causes. Green and Hoff (1937) and Hoff, Kell, Hastings, Sholes and Gray (1954) found in cats and monkeys that limb volume usually increased while kidney volume diminished during pressor responses evoked by electrical stimulation of the cerebral cortex. Peripheral stimuli due to tourniquet application in the limbs have also been shewn to cause reflex renal vasoconstriction.

The evidences presented in this chapter, showing the occurrence of reflex renal vasoconstriction in viscerovascular reflexes, is an addition to the existing lists.

Chapter III

It has been experimentally shewn that the changes in the splanchnic vascular bed can influence the peripheral resistance and the level of blood pressure (Ludwig and Thiry, 1864; Cyon and Ludwig, 1866; Jansen, Tains and Achetid, 1924; and Kramer and Wright, 1932).

But the vagi and the carotid sinus nerves carrying impulses from the baroreceptors to the vasomotor centre are primarily responsible for blood pressure homeostasis (Ludwig and Cyon, 1866; Hering, 1927; Heymans, Bouckaert and Regriers, 1933). These buffer nerves normally carry impulses which produce a depressor influence on the centre. So when these nerves are stimulated, there is a fall in blood pressure, and when the nerves are cut there is a rise in blood pressure.

From the observations in Chapters I and II, it can be stated that:-

- (i) After vagotomy and carotid sinus denervation, the rise in blood pressure following distension of the urinary bladder is much more marked.
- (ii) This vasomotor reflex response is abolished after bilateral splanchnicectomies.
- (iii) Reduction in renal volume and diminution in amplitude of renal pulses are more marked following vagotomy and carotid sinus denervation, and following splanchnicectomy no

evidence of renal vasoconstriction is obtained.

These findings indicate that in the presence of intact vagi and carotid sinus nerves splanchnic vasoconstriction and its effects shewn by the rise of blood pressure following the distension of urinary bladder, are less conspicuous.

Fig. 2, in Chapter II, shows that the renal pulses were smaller in size following vagotomy and carotid sinus denervation. Similar findings are obtained when the changes in renal volume and pulses are observed before and after denervation. Fig. 1 shows one of these results. It will be seen (Fig. 1) that the pulses became reduced to nearly half the size of the original (before denervation), and there was reduction of renal volume as well. Sixty per cent rise in blood pressure was obtained following bilateral vagal and carotid sinus denervation. In this animal, further reduction in renal volume and diminution in the size of renal pulses were obtained when the bladder was distended.

As the respiration always becomes slow following vagotomy and carotid sinus denervation, in later experiments the changes in renal volume and pulses were studied by using an artificial respirator. The rate of respiration was adjusted to 14-15/minute. Similar results, as discussed before, were obtained (Fig. 2). In these animals, reduction in the renal volume and pulses are observed when the urinary bladders were distended.

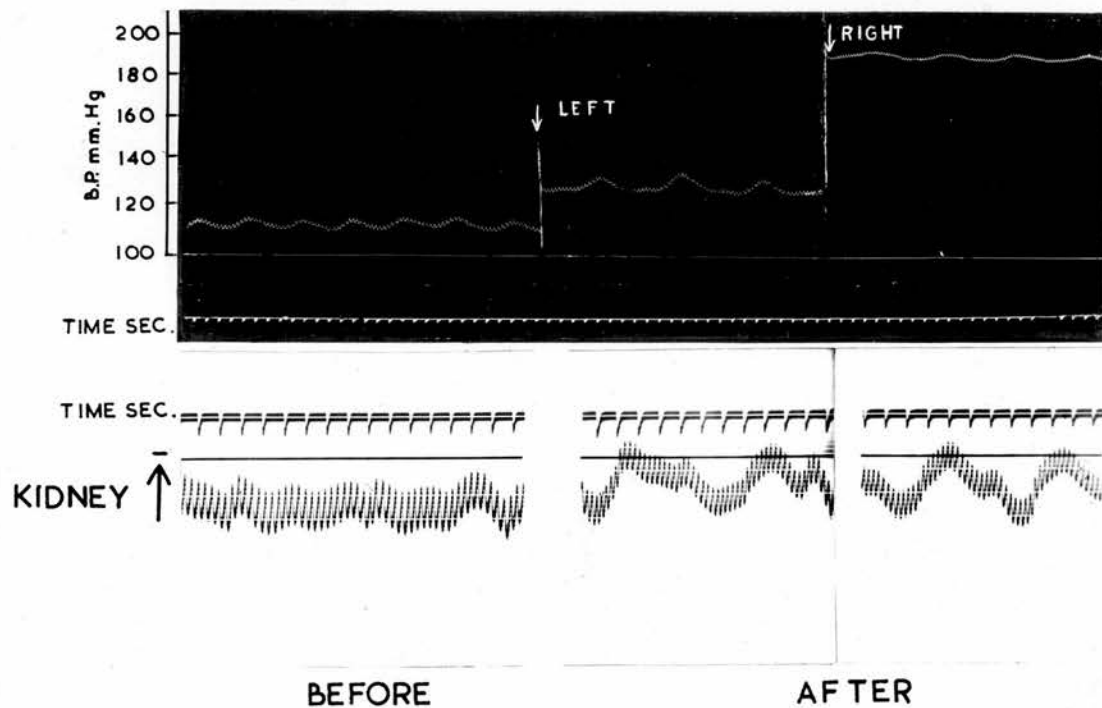


Figure 1

Upper tracing - blood pressure;
 lower tracing - renal pulses.
 Showing changes in the blood
 pressure and renal pulses and
 volume, before and after vagotomy
 and carotid sinus denervation.
 (Spontaneous breathing.)

↑ indicates decrease in volume

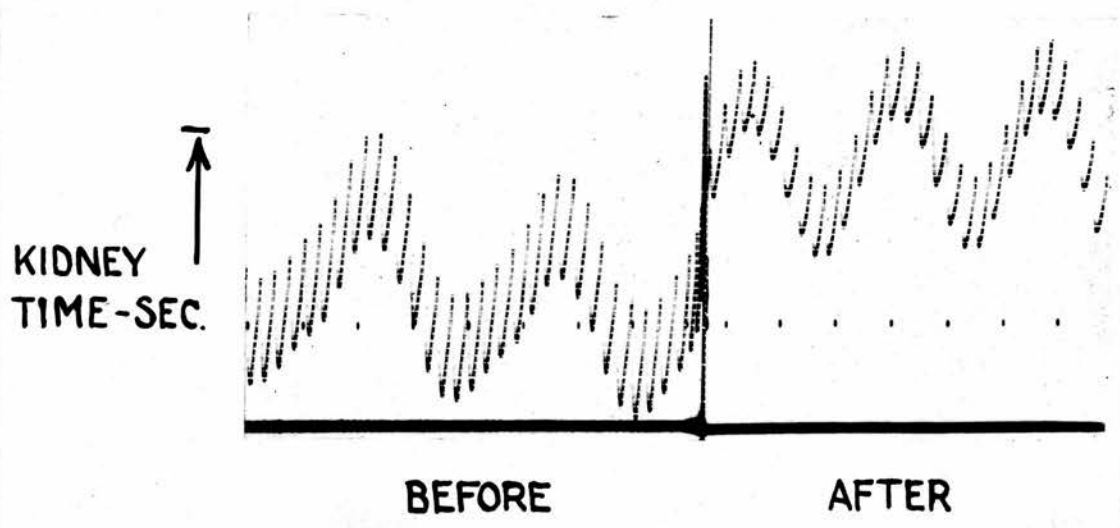


Figure 2

Changes in the renal pulses and
volume, before and after vagotomy
and carotid sinus denervation.

Therefore, it seems that normally the tonic (or vasoconstrictor) influence in the renal vascular bed is less in the presence of intact vagi and carotid sinus nerves. The increased tone (vasoconstrictor) following denervation may be due to increased excitatory influence or diminished inhibitory influence of the suprasegmental vasomotor centre to the splanchnic vasomotor mechanism (4D-2L). When the urinary bladder is distended, similar mechanisms come into play and so modify the reflex vasomotor responses. Very little, however, has been mentioned in the literature available about this interrelationship, in viscerovascular reflexes.

Izquierdo (1930) stimulated the peripheral end of the splanchnic nerves in anaesthetized rabbits, cats, dogs and hares, by a constant faradic stimulus under similar conditions, first with two sets of aortic and carotid sinus nerves intact, and then with these nerves partially or totally eliminated. He observed that when aortic and carotid sinus nerves are eliminated, the rise in blood pressure is always much more marked. Comparing the effects observed after elimination of both aortic nerves or both carotid sinus nerves alone, he found that the carotid sinus nerves exert the more important inhibiting effect upon the height of the curve. The observations of Izquierdo suggest that, when aortic and carotid sinus nerves are intact, the rise in blood pressure due to

splanchnic nerve stimulation can be compensated or counteracted to a considerable extent. Experimental evidence is needed to explain whether such control is by a compensatory vasodilation in the other parts of the body, or by a direct inhibition on the splanchnic vasomotor mechanism. As in acute spinal preparations (vide Chapter IV) following distension of the bladder, reflex rise in blood pressure and renal vasoconstriction can be obtained, almost of the similar pattern as in nonspinals (after denervation), it is worth while to investigate the above mechanism.

ACUTE SPINALS

Twelve cats have been used.

Preparation. The cat is anaesthetized, as described in Chapter I; the tracheal tube is put in: the animal is placed in the prone position, with a cotton bag under the clavicles, thus allowing the neck to be flexed slightly. The incision extends from a point in between the scapular spines up to the external occiput, at the midline. All dissections are carried out meticulously in the midline and thereby the bleeding is minimized. The skin, aponeuroses are all cut straight down to the spines. The muscles on the laminae are retracted on either side of the spines and for $\frac{1}{2}$ " off the lamina on each side, first by a few cuts with the scapel on the margins of the spines, and then by using its handle and a piece of gauze. The piece of gauze is kept for a minute or two and then taken out. The spine lying at the middle of the exposed area is removed. The root of the spine removed corresponds to T₁-T₂ level. The laminae are removed by nibbling from the centre to each side.

The spinal cord with the theca is exposed. The dura is always seen pulsating. Pulsating dura is a sign of good condition. The dura is then incised in the middle line for 1", and then a double loop of fine nonglazed linen threads is passed intradurally by a hook round the cord just above the middle of the space exposed. This

corresponds to C₈-T₁ level, usually. Now as the loops of the thread are tied, they cut through the spinal cord. Gently lifting the tied ends away from each other, the cut ends of the spinal cord are seen and a small piece of oxycel gauze is tucked in between, to help in haemostasis.

The whole preparation should not take more than 20 minutes, but at the same time precaution should be taken to start artificial respiration just before cutting the spinal cord. The rate of respiration employed in the present experiments is 15-17/minute.

After the spinal cord has been cut, the muscles are sutured loosely over it, a piece of gauze being used as a wick to drain from the spinal cord area to indicate whether any active bleeding is going on or not during the experiment. Then the skin and aponeurosis are sutured. The animal is very gently turned on its back.

The amount of bleeding in such preparations has never been more than 5-6 ml. The level of transection is always checked at the termination of the experiment.

At the beginning, it was considered that the low blood pressure in acute spinal shock following transection can be combated by infusion of Dextran (6% depolymerised dextran in 0.9% sodium chloride, supplied by Dextran Limited, Aycliffe, Darlington, England).

In two only, blood pressure could be raised from a level of 50 to 70 mm.Hg. by 10 ml. Dextran, injected slowly intravenously immediately following transection. In one the pressure remained at the higher level, but in the other it came down quickly to 40 mm., and subsequent infusion of Dextran did not have any beneficial effect. On the other hand, at each subsequent intravenous injection of dextran, a small rise in blood pressure with narrowing of the amplitudes of the pulses was evident. But it was quickly followed by a fall either to the same level or lower than before.

In the animal in which satisfactory results were obtained initially by the infusion of Dextran, it was later found that when the condition of the animal was growing worse by repeated distension of the bladder (which shall be discussed later in detail), further infusion of Dextran was of no value. Similar results as described before were obtained.

The fall in blood pressure in acute spinal preparations is undoubtedly due to extensive vasodilatation below the level of the lesion. The large and small vessels both participate in this vasodilatation (Wiggers, Glaser, Canavarro and Treat, 1943). An attempt was made to raise the blood pressure in acute spinal shock by either saline or Dextran or both. The author does not believe that by increasing the circulating fluid

it would be possible to raise the blood pressure satisfactorily and maintain it satisfactorily for any definite period.

The author's experience has been that the percentage fall of blood pressure following acute spinal transection from the level existing before transection has to be considered as an important factor. Usually the chloralosed cats have a high blood pressure for 30-40 minutes following chloralose administration. The author has found that, if the spinal dissection is done during this period, the bleeding is always more marked and the blood pressure comes down to very low levels, 40, 30 mm.Hg. immediately when the cord is transected. Whereas, if the spinal dissection is done 45-60 min. after the chloralose has been given, the bleeding is less and the blood pressure comes down to 60-70 mm.Hg. when the cord is cut. The rise of blood pressure to a higher level is quicker and more definite in the latter series. Following this observation, only one cat has been lost in the beginning of these experiments and none subsequently.

The temperature of the spinal animals is very difficult to control. A thermometer was left in the rectum and the heating of the table adjusted to that. The temperature should not be allowed to go up more than 37°C.

The author has always preferred to complete

the dissection of the exposure of the urethra, right femoral artery and the left kidney before starting the spinal dissection. These help in causing minimal handling to the spinal cat later on; all that is needed are to put in the cannulae to the urethra or femoral artery or to put the kidney in the plethysmograph, when the actual experiment with the filling of the bladder is to be started.

In some cases, vagi were also cut to produce identical condition as nonspinals (i.e. elimination of pressure receptors from arch of aorta and carotid sinus as well as any effector influence of heart in the reflex vasomotor responses).

Results

Studies in the changes in blood pressure

For the sake of convenience, the findings can be grouped as follows:-

(a) When the blood pressure is very low (below 40 mm.Hg.) and the animal is in a severe degree of acute spinal shock, no response is obtained on distending the urinary bladder, whatever pressure head and rate of distension are used. The big cutaneous veins, like the saphenous, remain empty at such stages.

(b) When the blood pressure is low (above 40

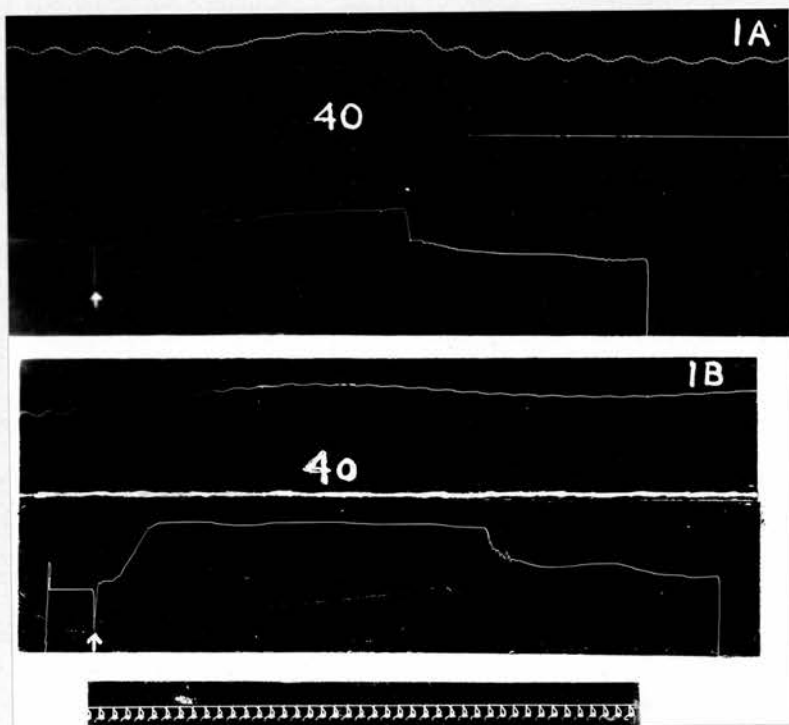
but below 60 mm.Hg.), a reflex rise of blood pressure is obtained, when the urinary bladder is distended at a pressure head of 65 or more mm.Hg., and also a much increased rate of distension (240-300 ml./min.) is used. But such responses are quickly abolished on repetition of the experiments, even when a higher pressure head or increased rate of distension is employed. (Figs 1A, 1B, 2A, 2B)

(c) When the blood pressure is above 60 (but below 90 mm.Hg.), a reflex rise in blood pressure (20-30%) can be obtained, on distending the urinary bladder at 65 mm.Hg. head at a rate of 120-240 ml./minute. Repeating the experiments, using the same rate of filling and same pressure head, the rise in blood pressure can still be obtained. But gradually such responses get poor. Then by increasing pressure head or rate of distension, a brisk response as obtained at the beginning can be produced. (Figs 3A, 3B, 3C)

(d) When the blood pressure is above 90 mm.Hg., almost identical responses, as discussed in post-denervation experiments in nonspinal preparations, are obtained (30-40% rise in blood pressure (Fig. 4)).

It has been found that, when the blood pressure rises, the amplitude of the pulse remains the same or is increased, if vagi are intact. But if the vagi are cut, the amplitude of the pulse gets smaller as the blood pressure rises. (Figs 2A, 2B)

Vagotomy did not influence the blood pressure



Figures 1A and 1B

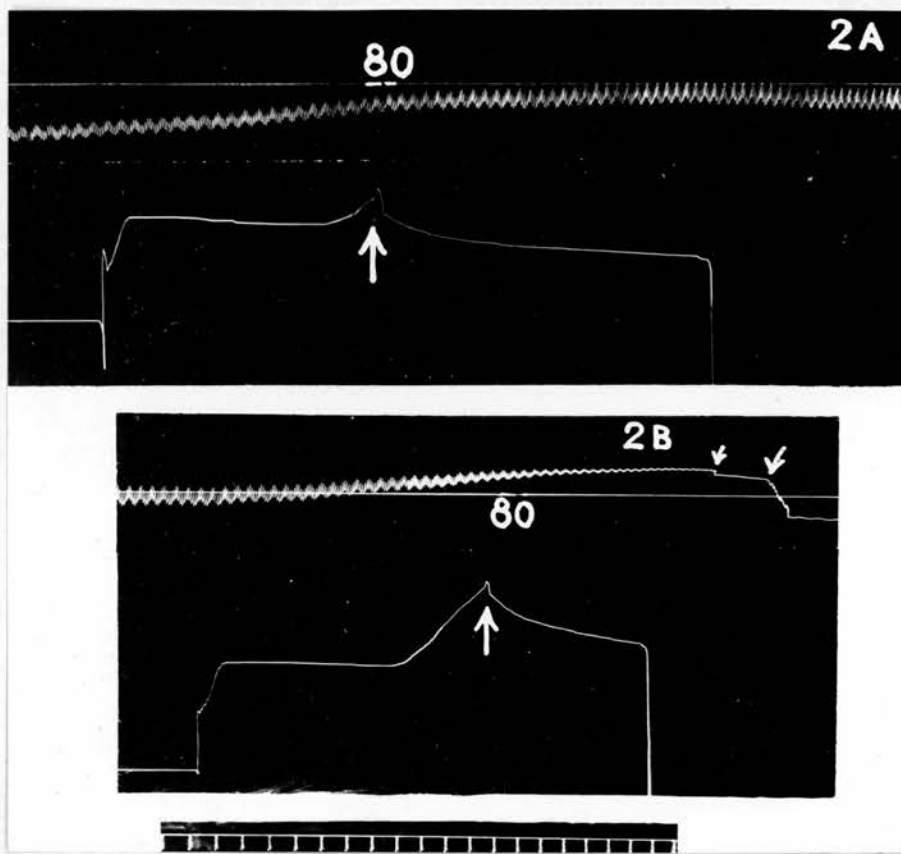
Blood pressure changes - upper tracing.

Bladder pressure changes - lower tracing.

(Time sec)

Note: On repetition, poor responses (rise in blood pressure). (Fig 1B)

Arrows indicate filling starts.



Figures 2A and 2B

Pressure changes - upper tracing.

Bladder pressure changes - lower tracing.

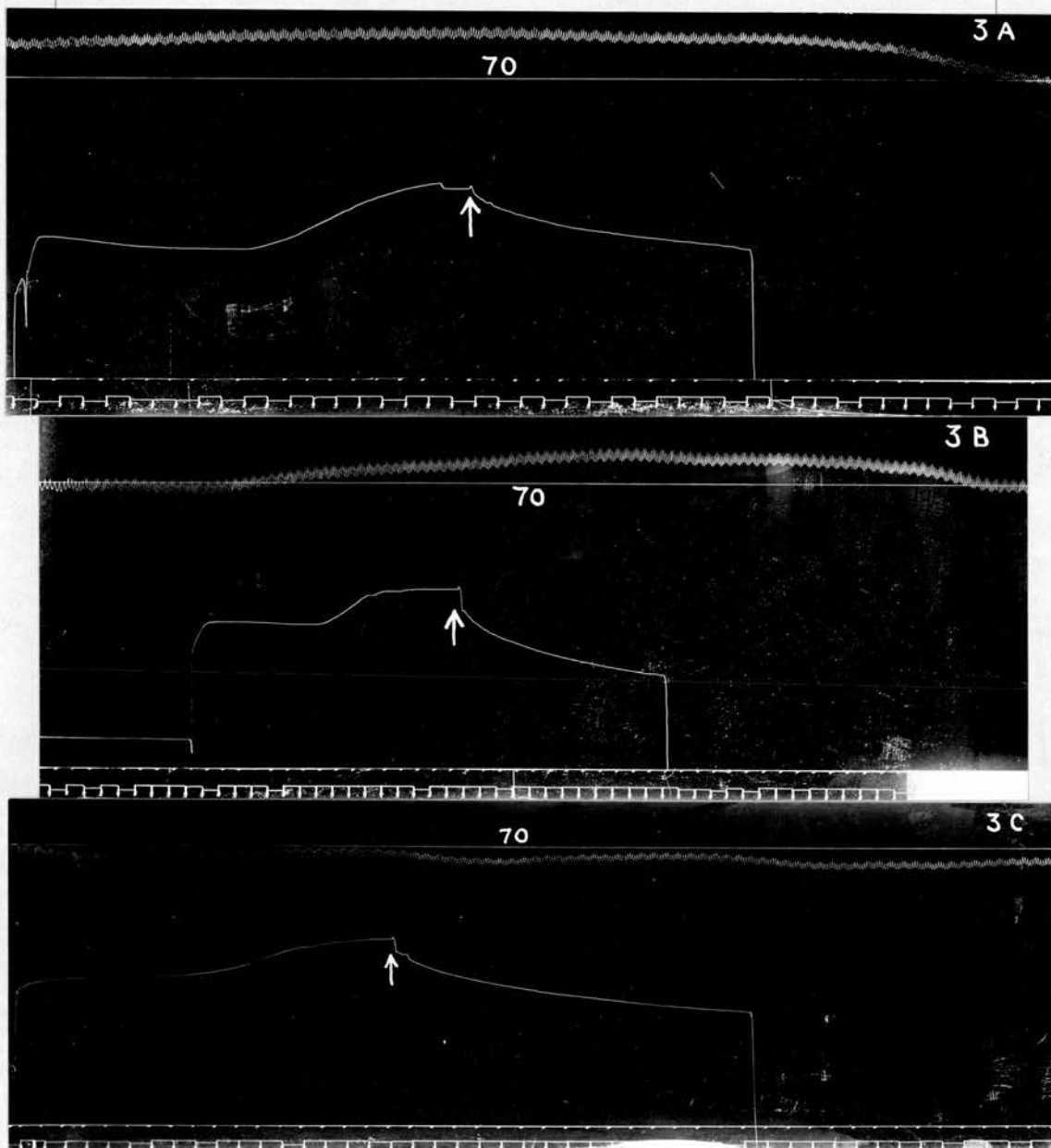
Figure 2A Before vagotomy.

Figure 2B After "

(Top) Arrows in Figure 2B signal where drums were stopped for $\frac{1}{2}$ minute each time.

(Below) Arrows indicate filling stopped.

(Time 5 secs)



Figures 3A, 3B, 3C

In each upper tracing is blood pressure.

In each lower tracing is bladder pressure.

(Time 5 seca)

(Figure 3C: Note that condition deteriorates and no response is obtained when bladder is distended repeatedly at quick intervals.)

SPINAL - AFTER BILATERAL VAGOTOMY

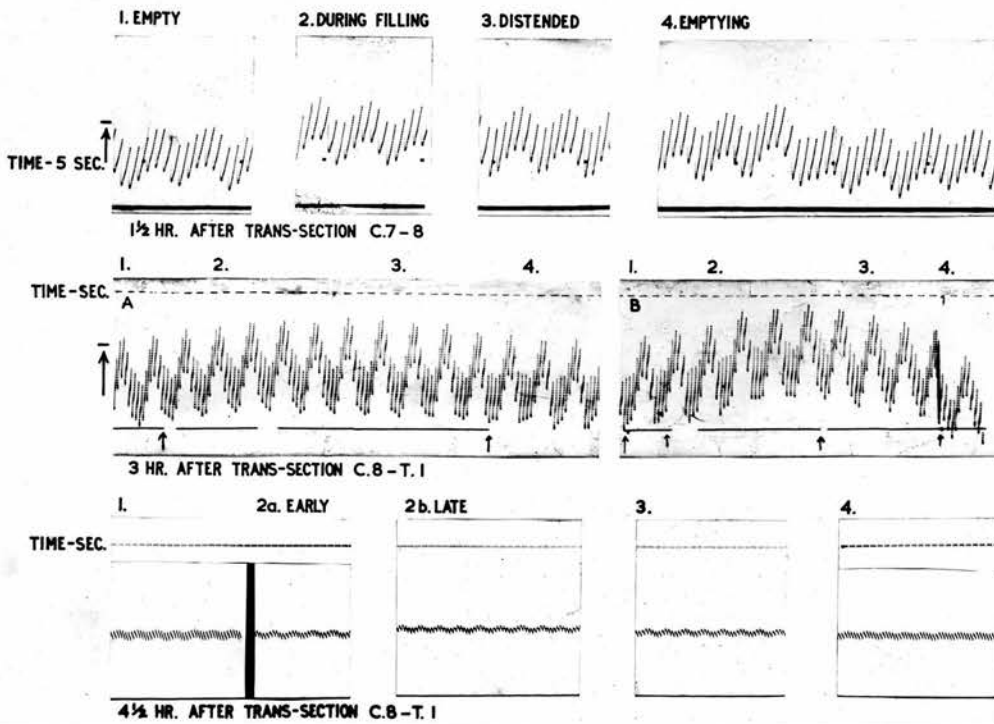


Figure 4

Shows the types of changes in renal pulses and renal vascular capacity.

The numerals at the top denote stages of bladder.

- 1 - Empty.
- 2 - Filling.
- 3 - Distended.
- 4 - Emptying.

The second tracing A and B show the varying degrees of vasoconstriction (reduction in renal volume) when different rates in filling the bladder were used.

- A - 120 ml./minute.
- B - 240 ml./minute.

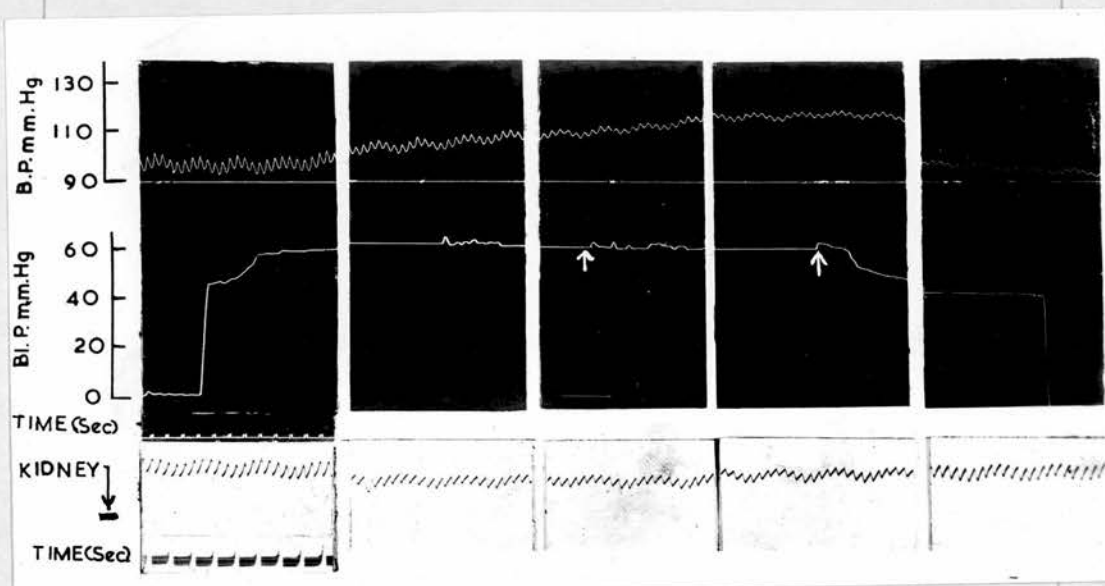


Figure 5

Upper tracing - blood pressure. (B.P.)
 Middle " - bladder " (Bl. P.)
 Lower " - renal pulses.

Changes in blood pressure and renal pulses as the urinary bladder is filled and kept distended and then emptied.

To note

- (1) B.I.P. First Arrow indicates Filling stopped
 Second Arrow indicates Emptying starts.
- (2) ↓ indicates decrease in volume

level that was obtained after spinal transection. Sometimes a little rise and sometimes a little fall was obtained for a short period. There is no definite parameter to predict when the animal will recover sufficiently from the state of shock and low blood pressure so that reflex vasomotor responses can be obtained satisfactorily. It is entirely a matter of trial. But it has always been found that to elicit vasomotor reflexes satisfactorily in acute spinal preparations, the animals must have a blood pressure at or above 60 mm.Hg. It is always better to leave the animal for 1-2 hours following the transection.

Changes in the renal vascular bed and renal pulses
(Fig. 4)

Both decrease in renal volume and diminution in the amplitude of renal pulses have been seen. It has been, however, a peculiar observation in the spinals that decrease of renal volume is more frequent than reduction in the pulses. When the reduction of pulses was obtained, no evidence of simultaneous decrease in volume was found and vice versa. It has been found that usually in the same animals, evidence of both decrease in volume and reduction in pulses can be obtained but the decrease in volume appearing first.

Undoubtedly, the changes in renal pulses or volume are not always very marked as in the nonspinal ones, but quite definite changes are

obtainable if the animal has got a blood pressure of 60 mm.Hg. or more.

Changes in paw volume

In one only it was attempted. No change was detectable. It was abandoned because it was found that it is very difficult to produce and maintain further vasodilatation by heating, over the vasodilatation obtained by spinal transection. Moreover, the regulation of temperature in animals in such stages of acute spinal shock is extremely difficult, and no definite prediction can be made as to how much the temperature variations can be resisted effectively without further detrimental influence on circulation.

General observations

In acute spinal preparations, it has always been observed that either a bigger pressure head or a quicker rate of distension has to be used to elicit the rise of blood pressure than that used in nonspinal preparations following vagotomy and carotid sinus denervation (when the blood pressure is below ⁹⁰/mm.Hg.).

By allowing the kymograph to move slowly, the changes in blood pressure and the amplitude of pulses were studied using 65 mm.Hg. pressure head and 60 ml./min. rate of filling the bladder (Fig. 4). It will be evident that the rise of blood pressure is continuous and steady but very slow.

When in the same animal a quicker rate is

used in distending the bladder, renal vasoconstriction becomes much more marked (Fig. 4).

These findings suggest that in acute spinal preparations, in states of hypotension, the stimuli to be effective have to be more powerful to cause "adequate" stretching of the bladder wall. It is so probably because the detrusor is hypotonic.

These findings are in agreement with those reported by Downman and McSwiney (1946-47).

Discussion

The observations of Sherrington in acute and chronic spinal animals regarding their reflex responses to exteroceptive and introceptive stimuli cannot be summarised here, even briefly. But one of the most remarkable contributions to the physiology from such observations is that the isolated spinal cord is capable of regulating vasomotor apparatus. By showing the rise of blood pressure following distension of ureter or common bile duct in the spinal preparations, he found also that the reflex response to visceral stimulation (in the isolated cord) is characterised by vasomotor reactions. Downman and McSwiney (1946-47) supplemented Sherrington's observations by showing similar reflex vasomotor responses to intestinal stimulation.

But the importance of such vasomotor reflex responses in chronic spinal conditions has only been realised lately (Guttmann and Whitteridge, 1947). Perhaps the role of autonomic nervous

system in the readjustment of regional distribution of blood in the body in chronic spinal conditions was visualized by Sherrington himself. (The Marshall Hall Prize Lecture adduces evidence to this.) But the distinctive role of individual vascular beds in the circulatory readjustments following visceral distension in chronic spinal men and animals has now been stressed (Whitteridge and his colleagues). The present observations in the renal vascular bed in acute spinal conditions confirm only one of the suggestions laid down by the above authors.

The splanchnic vascular bed in the spinal conditions (when the lesion is at lower cervical level) is not subject to suprasegmental influence. Though the vagi and the sinus nerves remain intact in spinal conditions, the isolated cord is free to act alone. Splanchnic vasoconstriction as a response to visceral distension can then precipitate a considerable rise in blood pressure. That such happens is shown in the findings of Guttman and Whitteridge (1947). The lower the spinal lesion, the poorer will be the reflex vasomotor responses. More of the spinal vasomotor unit will then be under control of suprasegmental influence. This is also illustrated in the findings of the same authors. The following problem then arises, whether the spinal vasomotor centres themselves possess both excitatory and inhibitory tones as the supra-

segmental vasomotor has. The report of Guttman and Whitteridge (1947) indicates that there may be transitory stages of low blood pressure and vasodilator response. Whether such responses are due to stimuli carried via the parietal sensory nerves and resultant axon reflexes have to be found out.

The effects of such rise in blood pressure on the bladder blood flow are under investigation. The difficulties encountered in studying circulation through intra-abdominal organs in acute spinal conditions are many. In an acute spinal state, the less the animals are handled, the quicker is the recovery. This is a great drawback to detailed study of splanchnic circulation as it necessitates intra-abdominal manipulation. In chronic spinal preparations, such difficulties may be overcome.

But the present findings support the hypothesis of Whitteridge and his colleagues that splanchnic vasoconstriction at least in renal bed does occur when the urinary bladder is distended in spinal conditions. The extent of the rise of blood pressure can be satisfactorily explained on the basis of interrelationship of suprasegmental and spinal vasomotor centres, (discussed in Chapter III.)

However, the fact still remains whether interception to blood flow occurs at aortic levels. The rise of blood pressure is primarily due to degree of obstruction of blood flow and, therefore, the

degree of interception. Perhaps cineangiography may throw a light on this aspect.

In clinical physiology, renal circulatory disturbances following spinal injuries have not been paid sufficient attention yet. The incidence of renal calculi following spinal injuries is considerable. It is worth investigating into such problems, too, in future, whether this is simply related to blood flow.

CONCLUSIONS

Studies in Viscerovascular Reflexes

In an anaesthetised cat, when the ureters are tied and the urinary bladder is distended, the blood pressure rises. A greater rise in blood pressure is obtained when the vagi are cut and the carotid sinuses are denervated. When the bladder is brought outside the abdomen and is distended, the rise in blood pressure can still be obtained. This response is abolished following bilateral splanchnicectomies.

When the left kidney is put within an egg cosy plethysmograph, and the changes in renal circulation are recorded optically by the use of a membrane manometer, evidences of renal vasoconstriction and diminutions of renal pulses are obtained on filling the bladder. Such changes in the renal circulation are always more marked following vagotomy and carotid sinus denervation.

In acute ^{high} spinal preparations, when the urinary bladder is distended, blood pressure rises and similar changes in renal circulation are observed. These findings are suggestive of:-

(i) A reflex pressor response is obtained when the urinary bladder is distended. It is primarily related to intravesical pressure, but it can be augmented by increased volume as well.

(ii) Splanchnic vasoconstriction is the pre-

dominant mechanism for the rise in blood pressure.

(iii) Renal blood flow is reduced as a reflex response to the distension.

(iv) To elicit such reflex vasomotor responses satisfactorily in nonspinal preparations, vagotomy and carotid sinus denervation are essential prerequisites.

(v) The reflex vasomotor responses due to stimuli arising in bladder can also be obtained in spinal preparations.

(vi) It appears that normally an inhibitory influence is exercised by the suprasegmental vasomotor centre over the splanchnic component of spinal vasomotor unit. The vagi and the sinus nerves form the afferent arc of this inhibitory mechanism. In spinals, the efferent fibres of the inhibitory mechanism are lacking and, therefore, viscerovascular reflexes may be exaggerated as a release phenomenon.

A. Comment on the Homeostasis of Blood Pressure

The role of baroreceptors in the homeostasis of blood pressure has been a subject of increasing attention by the physiologists and clinicians.

In recent years, the importance of vagi and carotid and aortic sinus nerves in this homeostasis has been re-emphasized by Heymans and his colleagues. The changes in mean arterial blood pressure have been found an effective stimuli for the receptors innervated by these nerves.

Gammon and Bronk (1935) have suggested that Pacinian corpuscles lying in mesentery in close relation to the mesenteric vessels may have some purpose in influencing the circulation in the splanchnic vascular bed. They have shewn that the effective stimuli to these receptors are related to the degree of distension of the mesenteric vessels rather than to the level of the mean blood pressure.

Heymans et al. (1936) suggested that the Pacinian corpuscles or such receptors situated in the periphery have normally little part to play in the homeostasis of blood pressure in general.

Taylor and Page (1951) have found definite evidence of baroreceptors in the pathway of cerebral circulation.

To investigate into the part played by the kidneys in the mechanism of hypertension, Page and McCubbin (1953) tried to find out whether there is any baroreceptor in the renal vascular bed. No

definite evidence has yet been obtained. But the autonomicity of the kidney in regulating its own blood flow suggests that there must be some physiological *modus operandi*.

The central baroreceptors (near the heart including those supplied by vagi and aortico carotid sinus nerves) are, no doubt, a pluripotent mechanism for the homeostasis of blood pressure in general. The findings of Edholm (1940) and Sinister and Conklin (1943) raise the possibility of the existence of subsidiary baroreceptors in the body. On the basis of the observations of Edholm, McDowall (1952) suggested that vasomotor centre (above spinal cord, suprasegmentally) responds directly to changes in blood pressure. Before such tentative conclusions could be reached, it will be necessary to prove that there is no other peripheral baroreceptor mechanism from which signal impulses can reach suprasegmental vasomotor centre when central baroreceptors are denervated.

In the paraplegics or in experimental spinal preparations, ^{with high lesions} the suprasegmental vasomotor centre has ~~got~~ no direct link with the segmental vasomotor units, except by the vascular system and the central receptors. The only way suprasegmental vasomotor centre can help in the homeostasis of blood pressure will be by controlling the heart. But the maintenance of the effective circulating blood volume is important for a healthy life. The

alterations in the pumping of the heart may not affect the cardiac output (Whitteridge and his colleagues). In these conditions with venous pressure rising and heart rate falling, in fact cardiac output does not go up, In such cases, the peripheral resistance freed of suprasegmental vaso-motor control becomes the determining factor for the rise of blood pressure. When the pressure rises, the heart beats slowly and strongly to compensate ^{the} for/increased load and thus to its own benefaction as by such mechanism coronary blood flow will be increased and the cardiac musculature can stand the increased peripheral resistance for a longer period. This is done by means of intact vagi. If the blood pressure rises too high, the cerebral vessels can be prevented from any continuously increasing stretching effects by diversion of blood to the nearest vessels, i.e. the vessels of upper limbs. The important and closely coordinated working of sympathetico-adrenal system may be a possibility in this working adjustment. It may also be due to narrowing of a segment of aorta below the origin of the subclavian arteries - the degree of narrowing being such as to cause a sudden but sustained rise of pressure proximally.

In such conditions, the role of Pacinian corpuscles may be considerable. Do these receptors now help in the redistribution of blood? We no not know yet, but in the future it will be

worthwhile to investigate into it. The question then arises how much significant these peripheral receptors are in the presence of central receptors. The answer is difficult as the biological role of different structures to be assessed, requires a careful analysis of the functional variations of the species, chronologically, from the lower to the higher forms obtained in evolution.

B. Comment on the Viscerovascular Reflexes in relation to Homeostasis of Blood Pressure

The hollow viscera and the blood vessels lined by smooth muscles have one common function to serve, i.e. to permit the passage of the contents forwards. Some of these structures, like the stomach, the intestine from the lower ileum to rectum, the gall bladder and the urinary bladder, are also accustomed to accommodate the contents and, therefore, to a certain amount of stretch. But the rest are functionally mere conduits. This is probably the reason why the quanta of stimuli to produce the same reflex responses differ in different portions of the gut. It is recognised that the upper part of intestine has a greater tone, irritability and a faster rhythm than the lower part (Houckgeest van Braam, 1872; Floel, O., 1885; Luderitz, C., 1889; Biedermann, W., 1905; Alvarez, 1914; Schragar and Ivy, 1928; ~~Zoolinger, R., 1933~~; Irving, McSwiney

and Suffolk, 1937; Svien and Mann, 1943). When there is obstruction to the passage of contents, the part proximal to the obstruction gets distended and stretched. When the threshold of stretching reaches a limit, reflex responses occur. Sherrington first conceived that pain is only one of the manifestations of visceral distension and it is entirely a function of suprasegmental neuraxis. When the suprasegmental control or machine is disconnected from the infrasegmental neuraxis, vasomotor reflex responses play a dominant role. Even in the integrated nervous system, such responses may and do manifest themselves. This shows that the central baroreceptors perhaps play a double role in (i) homeostasis of blood pressure, (ii) controlling viscerovasomotor reflexes and thus allowing suprasegmental neuraxis to concentrate on exteroceptive impulses.

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